Medical Library

DECEMBER, 1945 Vol. 122, No. 6

ANNALS of SURGERY

A Monthly Review of Surgical Science and Practice

CONTRIBUTIONS IN THIS VOLUME

IN HONOR OF

DALLAS BURTON PHEMISTER

J. B. LIPPINCOTT COMPANY

When a "SPINAL" is a "MUST"

Almost three decades have passed since NEOcaine's introduction for spinal anesthesia. Its low toxicity and numerous advantages encouraged wide use, but it remained for clinical experience to bring into clear, sharp outline the preferred indications for NEOcaine.

NEOcaine is used for operations below the diaphragm.

NEOcaine is preferred (1) when pulmonary disease makes inhalation anesthesia questionable, (2) for extensive, shock-inducing surgery, (3) in cardiac, renal, diabetic or thyroid disease, (4) in toxemias and (5) for the aged.

NEOcaine involves less visceral manipulation and packing-off. The abdomen is "silent" and relaxed.

NEOcaine minimizes postoperative discomfort, toxemic sequelae and secondary shock.

Administration: Employ 1 mg. of NEOcaine per pound of body weight, up to 150 mg. Dissolve crystals with spinal fluid led into the ampoule. Inject slowly with optional barbotage, using a 22 gauge needle. Trendelenburg at once, continuing for 3 hours. Contraindicated in gastrointestinal perforation, obstruction, peritonitis, cerebrospinal or dorsal skin disease. Drug idiosyncrasy is rare.

NEOCAINE

1917-1945

SUPPLIED: Ampoules of 50, 80, 100, 120, 150, 200, 300 mg. of pure procaine hydrochloride. Boxes of 10.

ANGLO-FRENCH LABORATORIES, Inc.

75 VARICK STREET, NEW YORK 13, N. Y.

THE USE OF BLOOD PLASMA FOR FILLING THE PLEURAL SPACE FOLLOWING TOTAL PNEUMONECTOMY*

A CLINICAL STUDY

W. E. Adams, M.D., T. F. Thornton, Jr., M.D.,
AND
L. M. Carlton, Jr., M.D.
Chicago, Ill.

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF CHICAGO, CHICAGO, ILL.

Since Graham's[1] successful removal of an entire lung for bronchogenic carcinoma in 1933, surgical treatment of this tumor has enjoyed marked success. In a recent article by Rienhoff,[2] who reviewed his own series of 181 consecutive cases, and reported on the results of a number of other surgeons, it was found that the mortality for this operation has been reduced to an average of 20 to 25 per cent, and in some instances as low as .66 per cent. Most of the technical difficulties of the procedure have been overcome, the principle causes of fatality being some form of infection or cardiorespiratory failure. A fairly high percentage of patients with this lesion are in the sixth or seventh decade of life. Therefore, a marked lowering of reserve in the cardiorespiratory function is present. Thus, in these patients an infection that otherwise might be relatively unimportant may be sufficient to result fatally.

In Graham's first patient, following the removal of the lung, a seven-rib thoracoplasty was made for obliteration of the pleural space. This was performed for a number of reasons, not the least of which was to avoid the danger of a serious empyema. Subsequent experience has demonstrated that total ablation of one lung may be performed without thoracoplasty, and that a serosanguineous fluid coming from the adjacent tissues fills the residual cavity. At the present time most pneumonectomies are made without thoracoplasty, although the procedure of choice continues to be controversial.[3] The chief objections to pneumonectomy without thoracoplasty have been: (1) the hazard of serious infection of the pleural space and mediastinum; and (2) the ill effects produced by overexpansion of the remaining lung. A third, and seldom considered undesirable effect of this method, is the lowering of the blood plasma protein and tissue protein reserve, which is partly due to the filling of the remaining pleural space with fluid rich in proteins.

* This work was supported in part by a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

The rate of filling this space following pneumonectomy is quite variable, depending upon the vascularity of severed adhesions, and the amount of operative trauma. It may be quite rapid, especially where sulfonamides are used locally in the pleural cavity at the site of operation. The rate of filling is probably also increased by the negative pressure in the pleural cavity.

The accumulated pleural fluid has been analyzed and found to contain approximately 4 to 5 Gm. per cent of proteins, somewhat less than that normally contained in blood plasma. Since this space usually has a capacity of between 700 and 1,000 cc., the amount of proteins removed from the circulating blood and, thus, from the protein reserve of the tissues is considerable. The degree of ill effects of rapid depletion of proteins from the circulation and tissue reserve will depend upon (1) the status of tissue proteins preceding operation; and (2) the adequacy of replacement of blood loss during and following the surgical procedure. Although at the present time there is a better appreciation of the severity of blood loss accompanying intrathoracic operations, recent studies have indicated that these patients do not usually receive sufficient replacement therapy for maintaining the blood in the preoperative status.

The ill effects of hypoproteinemia on the surgical patient have been investigated in recent years. Extensive studies on both animal and man reveal a striking parallel between the incidence of postoperative infections and delayed healing of wounds, and the presence of subnormal blood proteins. Thompson, Ravdin and Frank[4] produced hypoproteinemia in dogs and found that the repair of wounds was delayed in these animals. In further experiments[5] delayed healing was averted by the restoration of blood proteins to a normal level immediately following operation.

In a study of postmortem material, including both medical and surgical conditions, Cannon, and his associates,[6] showed a definite relationship between protein deficiency and the incidence of serious infection. The explanation for this was found in the lowered concentration of antibody globulin in protein deficient rats, demonstrated by immunologic and chemical methods.[7] In further investigations on rabbits they found that a diminution of agglutinins produced an increased susceptibility to infection in the presence of hypoproteinemia as compared to litter mates with normal blood protein levels.

In view of the hazard of infection in the pleural cavity following pneumonectomy and its relationship to protein deficiency, at the suggestion of Doctor Phemister, some experiments were planned to test the effect of filling the pleural space with blood plasma following the removal of an entire lung in animals.[8]

In experiments performed on 61 dogs and four goats, complete blood studies were made before and after the resection of an entire lung. In one group no transfusions were given following the operation, and the pleural cavity was allowed to become obliterated spontaneously. In the second group, replacement of blood cells and plasma lost both during operation, and

into the pleural space following operation, was made by the transfusion of plasma or by whole blood. In the third group, the replacement therapy was entirely made by the use of blood plasma or serum which was placed in the pleural cavity at the end of the operation. The results of the control experiments revealed that the total blood proteins were reduced by as much as 25 to 30 per cent of their preoperative value. This reduction placed the blood proteins at a significantly low level of 4 to 5 Gm. per cent, and the preoperative level was not regained for approximately ten days, the period of wound healing. Several factors were thought to be contributory in producing the reduction of proteins, namely, removal of lung tissue, the thoracotomy wound, infection, and the lack of nitrogen balance.

Replacement therapy in the form of blood or serum given intravenously, or serum intrapleurally, was quite effective in reducing the amount of blood protein fall after pulmonary resection. If given in sufficient amounts, both methods of administration appeared to be quite effective.

In view of the above results it was decided to make a clinical study of the changes in blood proteins following various operations on the thorax.[9] Blood protein determinations, made by the micro-Kjeldahl method,[10] and hematocrit values were obtained before and at two-day intervals for a ten- to 14-day period after 32 major operations including: lobectomy, 14; pneumonectomy, five; exploratory thoracotomy, seven; and miscellaneous, six. From these investigations it was found that the blood plasma proteins fell approximately 1 Gm. per cent following these operations, and occurred in 31 of the 32 instances. This fall occurred in spite of the fact that the blood lost at operation was thought to have been fairly adequately replaced. The range of fall for the 14 lobectomies was from 0.44 to 2.91 Gm. per cent, the lowest blood protein level usually being on the fourth or fifth day following operation. In approximately one-third of the entire series of 32 patients the fall was below the danger level of 5.50 Gm. per cent. The average transfusion for this group of patients was 942 cc. at operation and an additional 782 cc. during the period of convalescence. The fall in protein level was ascribed to operative blood loss, loss of blood and serum into the wound and pleural cavity following operation, infection, diminished protein reserve, and inadequate replacement therapy. Transfusion of whole blood was thought to be the most satisfactory single therapeutic agent when blood proteins were lowered due to loss of blood.

In view of the results of the above studies, it was thought worth while to test the influence of filling the pleural space with plasma following total pneumonectomy in man. This report is based on results obtained in 18 patients receiving such treatment, and ten additional patients used as controls in whom no plasma was employed. The usual method of management was as follows: Prior to operation the red cell count, hemoglobin value and plasma protein level were determined. If preoperative transfusions were required the tests were repeated following the transfusion. At the time of surgery between 500 cc. and 600 cc. of blood plasma were introduced into the pleural

TABLE I

ALTERATION OF THE BLOOD FOLLOWING TOTAL PNEUMONECTOMY—USE OF PLASMA FOR FILLING THE PLEURAL SPACE

Case and Init.	At Operation: Plasma in Pl. Cav.	At Operation: Blood Transfusion	Blood Studies	Preop.	Days Postoperative: 1	2	3	4	5	6	7	8	9	10 to 15	Remarks
1	0	500 cc.	R.B.C.	4.5										4.7	No infection.
C. C.		1 day PO	Hb.	14.0										13.0	
		+500 cc.	P.P.												
		4 days PO													
2	0	500 cc.	R.B.C.	4.8						4.3				4.0	No infection.
H. R.			Hb.	12.0						13.0				10.0	Died 9 mos. PO of ruptured appendix and peritonitis.
			P.P.												
3	0	600 cc.	R.B.C.	4.6			5.0		4.5						Died 6 days PO of heart failure. No infection.
P. Q.		+500 cc.	Hb.	12.0			14.0		14:0						
		5 days PO	P.P.												
4	0	500 cc.	R.B.C.	4.2	4.4			4.1				3.5		4.3	Died 5 wks. PO of infection of pleural and pericardial cavities.
S. L.		+500 cc.	Hb.	16.0	14.0			13.0				14.0		13.5	
		3 days PO	P.P.												
5	0	500 cc.	R.B.C.	4.6		5.2			4.9			5.5	4.9		Died 11 days PO. Pneumonia, bronchial fistula with empyema.
F. F.		+500 cc.	Hb.	12.0		13.0			15.0			15.0	12.0		
		1 day preop.	P.P.												
6	0	750 cc.	R.B.C.	4.9	4.4	4.9	4.0	4.6		4.4	4.4		4.2		Pleural fluid protein = 4.1—4.3 Gm. %.
R. T.			Hb.	15.5	14.4	13.5	13.1								
			P.P.	7.4		5.9	5.9			6.4		6.9		6.7	
7	0	2650 cc.	R.B.C.	4.8	5.0		4.8		4.5		5.9			5.1	Bronchitis and atelectasis. Died 13 days PO of sulfa-anuria.
J. K.		+500 cc.	Hb.	12.5	16.5		13.0		14.3		16.0			14.0	
		Plasma	P.P.	6.4	6.0	5.5	5.4	5.0	5.2			5.4	5.6	5.8	Pleural fluid protein = 4.2—4.7 Gm. %.
		9 days PO	Hmt.	36.0	49.0	45.0	48.0	44.0	46.0			44.0		46.0	
8	0	1000 cc.	R.B.C.	3.8	3.4				4.1		4.0			4.2	Pleural fluid protein = 4—4.3 Gm.
L. R.	Sulfathiazole	+300 cc.	Hb.	11.0	12.0				11.5		13.0			14.0	Bronchial fistula and empyema. Thoracoplasty.
	1 Gm.	plasma	P.P.	6.8	6.1	5.7	6.1	5.9	6.2	6.4	6.1			6.6	
		+500 cc.													
		3 days PO													
9	0	1500 cc.	R.B.C.	4.2	4.1					4.2				4.0	Pleural fluid protein = 4.4 Gm. %. Bronchitis and atelectasis. Pneumonia.
M. K.	Sulfathiazole		Hb.	12.5	14.0					13.5				13.0	
	2.5 Gm.		P.P.	6.2					5.02					6.0	
10	0	1500 cc.	R.B.C.	5.0	4.9			4.6	4.47					4.8	Stormy PO course, with bronchial secretions and pneumonitis.
A. H.			Hb.	15.0	16.4		13.8	13.8	14.1			14.2		15.0	
			P.P.	7.2	6.1		5.3	5.0						5.9	

Annals of Surgery December, 1945

Case and Init.	At Operation: Plasma in Pl. Cav.	At Operation: Blood Transfusion		Preop.	1	2	3	4	5	6	7	8	9	10 to 15	Remarks
10	0	1500 cc.	R.B.C.	5.0	4.9			4.6	4.47					4.8	Stormy PO course, with bronchial secretions and pneumonitis.
A. H.			Hb.	15.0	16.4		13.8	13.8	14.1			14.2		15.0	
			P.P.	7.2	6.1		5.3	5.0						5.9	

TABLE I—(*Continued*)

ALTERATION OF THE BLOOD FOLLOWING TOTAL PNEUMONECTOMY—USE OF PLASMA FOR FILLING THE PLEURAL SPACE

Case and Init.	At Operation: Plasma in Pl. Cav.	At Operation: Blood Transfusion	Blood Studies:	Preop.	Days Postoperative: 1	2	3	4	5	6	7	8	9	10 to 15	Remarks
11*	600 cc.	2400 cc.	R.B.C.	7.1	5.7		5.8	6.0		5.1			5.2	4.9	Pleural fluid protein = 5—5.2 Gm. %.
R. R.	Sulfathiazole	plasma	Hb.	24.0	16.5		16.0	17.0		15.0			16.0	17.0	No infection. 800 cc. Pl. I.V. and 350 cc. Pl. I.P. 2 days PO.
	5 Gm.		P.P.	5.3	5.6	5.5		5.8	5.6		6.0			6.3	
12	600 cc..	1500 cc.	R.B.C.	4.1			4.0		4.2						Pleural fluid protein = 4.4—5 Gm. %.
G. S.	2 days PO	+500 cc.	Hb.	12.2			14.0		14.8						Empyema and bronchial fistula 6 wks. PO.
	Sulfathiazole	1 day preop.	P.P.	6.3	6.5	6.1	5.7	5.5		6.0		6.2		6.5	Thoracoplasty.
	2 Gm.														
13	300 cc.	2500 cc.	R.B.C.	4.1		3.7			4.0			4.1			300 cc. red cells 8 days PO. No infection.
M. H.	Sulfathiazole	+500 cc.	Hb.	14.0		12.5						12.0			Died about 9 mos. PO of metastases.
	5 Gm.	3 days PO	P.P.	7.4	6.9	6.5	5.8	6.2	6.2	6.8	6.9	7.2	6.9		
14	500 cc.	500 cc.	R.B.C.	4.5											Died 3rd day PO of massive pulmonary em-
B. W.			Hb.	13.5											bolism. No infection.
			P.P.		6.1										
15	500 cc.	500 cc.	R.B.C.	5.3	4.2						3.9			4.6	Pleural fluid protein = 4.8—5 Gm. %. No
S. G.	Sulfathiazole	+500 cc.	Hb	14.0	14.5						13.0			13.0	infection, temporary bronchial fistula.
	5 Gm.	plasma	P.P.	7.6				5 9							
16	600 cc.	1500 cc.	R.B.C.	5.7		5.2		4.8		5.4	5.9		5.6		Pleural fluid protein = 4.5—5.5 Gm. %.
C. S.	Sulfathiazole		Hb.	17.2		15.2		14.0		14.0	15.4		15.5		No infection.
	5 Gm.		P.P.	7.0	6.7	5.2	5.8			5.4			5.9	6.4	
17	500 cc.	1000 cc.	R.B.C.	3.3	4.3										Died 2 days PO of massive pulmonary em-
R K.			Hb.	10.0	11.5										bolism.
			P.P.	6.2	5.7										
18	600 cc.	1500 cc.	R.B.C.	4.0	4.6	5.2	4.5	3.5				4.1	3.8	4.6	No infection. Died 4.5 mos. PO of cerebral
R. C.		+500 cc.	Hb.	11.0	12.0	15.0	10.4	11.0				12.5	12.0	12.3	metastases?
		7 days PO	P.P.	6.1	5.7			5.1		5.6				5.9	
19	550 cc.	1500 cc.	R.B.C.	4.9			5.0		5.1			4.6		5.1	No infection except an abscess of chest wall,
H. S.	+200 cc.	+500 cc.	Hb.	14.5			14.4		14.4			11.2		13.0	5.5 mos. following operation.
	2 days PO	7 days PO	P.P.	6.5							5.8			6.3	
20	500 cc.	1500 cc.	R.B.C.	5.1	5.0	5.4	5.4				4.0			5.0	No infection.
A. J.	+500 cc.		Hb.	16.0	14.3	14.3	14.3				14.0			15.5	
	3 days PO		P.P.	6.2	5.8						5.8			6.1	
	200,000 P.														
21	500 cc.	1000 cc.	R.B.C.	4.6	4.6			3.8			5.5			4.7	No infection.
N. Mc.	+300 cc.		Hb.	12.0	13.6			11.3			14.4			13.7	
	3 days PO		P.P.	5.7	5.5		5.6				5.2				
	200,000 P.														

Volume 122 Number 6

TABLE I—(*Continued*)

ALTERATION OF THE BLOOD FOLLOWING TOTAL PNEUMONECTOMY—USE OF PLASMA FOR FILLING THE PLEURAL SPACE

Case and Init.	At Operation: Plasma in Pl. Cav.	At Operation: Blood Transfusion	Blood Studies: Preop.		Days Postoperative: 1	2	3	4	5	6	7	8	9	10 to 15	Remarks
22	600 cc.	1000 cc.	R.B.C.	4.5	4.7			4.2					4.1	3.3	No infection.
P. C.	+400 cc.	+1000 cc.	Hb.	13.0	13.5			11.5					12.8	11.8	
	3 days PO	9 days PO	P.P.	7.1				5.9					5.7	6.1	
	200,000 P.														
23	550 cc.	1000 cc.	R.B.C.	5.0	4.9		5.1		5.3			4.5		4.4	No infection.
F. K.	+450 cc.		Hb.	13.5	13.0		13.5		14.0			13.0		12.0	
	4 days PO		P.P.	7.4	7.3		6.0		6.4					6.6	
	200,000 P.														
24	550 cc.	1500 cc.	R.B.C.	4.5	4.9							4.7		4.5	No infection.
J. N.	+250 cc.	+500 cc.	Hb.	11.0	13.5						12.5			10.5	
	4 days PO	8 days PO	P.P.	5.6		5.4				5.1				5.1	
	200,000 P.		Hmt.	33.2	41.0	39.8	40.4		39.5			38.4			
25	550 cc.	1000 cc.	R.B.C.	4.8	4.3			4.3		4.7	3.8			4.3	Pleural fluid protein = 4.6 Gm. %.
M. B.	200,000 P.		Hb.	13.2	13.0			12.3			12.3			13.0	
			P.P.	6.4			5.9								
			Hmt.	40.2	41.3			37.7			36.3				
26	550 cc.	1000 cc.	R.B.C.	4.9	4.7										Died 3rd day PO of bronchial asthma and
H. W	200,000 P.		Hb.	13.8	12.4										cardiac failure. No infection.
			P.P.	7.2											
27†	550 cc.	1500 cc.	R.B.C.	4.8	4.8		4.9					4.6		4.4	No infection.
A. C.	200,000 P.		Hb.	13.0	13.5		13.5					13.0		13.0	
			P.P.	7.7	7.0		8.0	7.2						7.4	
28	550 cc.	1500 cc.	R.B.C.	4.8			4.9		5.0						Pl. fluid prot. = 4.95—5.21 Gm. %. Died.
O. S.	+250 cc.		Hb.	12.6			13.6								5 days PO of bronchial pneumonia. Vital
	1 day PO		P.P.	7.4					7.1						capacity 1700.
	200,000 P.														

Detailed results of blood studies before and following total pneumonectomy in 28 cases.
The complications and blood determinations on pleural fluid are indicated under remarks.
Abbreviations: R.B.C. = Red blood cells.
Hb. = Hemoglobin.
P.P. = Total blood plasma proteins.

* This patient had an arteriovenous fistula of the left lung for which total pneumonectomy was performed.
† This patient had a chronic diffuse pneumonitis for which a total pneumonectomy was performed.

cavity at closure of the thoracic wall. In addition to the plasma, 200,000 units of penicillin were placed in the pleural space in nine of the 18 patients.

Between one and three days after operation, following chest fluoroscopy, the remainder of the residual air was removed and replaced with plasma, usually 200 to 400 cc. Immediately following operation and for a period of two to three weeks, additional analyses of the blood were made at intervals of one to three days.

In addition to the above studies, fluid was obtained for plasma protein determinations, culture, and penicillin concentration from the pleural cavity in both the control and the treated groups.

RESULTS

Detailed results of these studies are seen in Table I. In analyzing this data one should keep in mind that an attempt had been made, in most patients, to replace the entire amount of estimated blood lost at operation by blood transfusion during and immediately following the operation. For this reason surgical shock was practically never observed.

From the data presented, and also from studies as yet unpublished,[11] it was evident that the greatest drop in red cell count, hemoglobin and hematocrit occurred between the third and fifth day after surgery. Following this there was a slow return to normal, but in most instances the preoperative plasma protein level had not been reached by the end of two weeks postoperatively.

The lowering of blood plasma proteins was also usually greatest by the third to fifth day but the fall did not always parallel that of the hemoglobin. In some patients the red cell count and hemoglobin remained very nearly the preoperative level, although the plasma proteins fell. (See Cases Nos. 7 and 16.) When the proteins were lowered to a considerable degree, *i.e.*, by 1 to 1.5 Gm. per cent, they usually had not returned to the preoperative level by the end of two weeks following operation.

Table II and Graph I present the changes in blood plasma proteins following pneumonectomy. The range of lowest level of proteins following operation is indicated in A of Table II, the largest number of patients averaging between 5 and 6 Gm. per cent. However, three patients in Group II did not fall below 6 Gm. per cent.

The range of plasma protein fall following surgery is indicated in B of Table II. Nine of the 14 treated patients (Group II) fell less than 1.4 Gm. per cent, two others were between 1.4 and 1.7 Gm. per cent. The three remaining patients (Nos. 13, 15 and 16) all received sulfathiazole locally in the pleural cavity at the time of operation. This resulted in a marked accumulation of pleural fluid. In patient No. 16, 680 cc. were removed to relieve a serious mediastinal shift. In patient No. 13 a large amount of serum drained out through the chest wound. The third patient had inadequate replacement of blood loss by transfusion. Thus, there is adequate explanation for the marked lowering of plasma proteins in these three cases. In the control group (I) the fall in plasma proteins ranged from 1 to 2.1 Gm. per cent, none of

* This patient had an arteriovenous fistula of the left lung for which total pneumonectomy was performed.
† This patient had a chronic diffuse pneumonitis for which a total pneumonectomy was performed.

TABLE II

BLOOD PROTEIN ALTERATION FOLLOWING PNEUMONECTOMY

Blood Plasma Protein Fall Following Operation	Group I No Plasma Placed in Pleural Cavity	Group II Pleural Cavity Filled with Plasma
A. Range of lowest level of plasma proteins:	Patients— Total and Case Nos.:	Patients— Total and Case Nos.:
5.0—5.4 Gm. %	3 (7, 9 & 10)	4 (16, 18, 21 & 24)
5.5—5.9 Gm. %	2 (6 & 8)	7 (12, 13, 15, 19, 20, 22 & 25)
6.0—6.4 Gm. %	0	1 (23)
6.5—6.9 Gm. %	0	0
7.0—7.4 Gm. %	0	2 (27 & 28)
B. Range of fall of plasma proteins:	Total and Case Nos.	Total and Case Nos.:
0.3—0.5 Gm. %	0	5 (20, 21, 24, 25 & 28)
0.6—0.9 Gm. %	0	3 (12, 19 & 27)
1.0—1.3 Gm. %	2 (8 & 9)	1 (18)
1.4—1.7 Gm. %	2 (6 & 7)	4 (13*, 15†, 22 & 23)
1.8—2.0 Gm. %	0	1 (16‡)
Over 2.0 Gm. %	1 (10)	0
C. Avg. fall	1.48 Gm. %	0.9 Gm. % for 14 patients 0.77 Gm. % for 11 patients (See below)

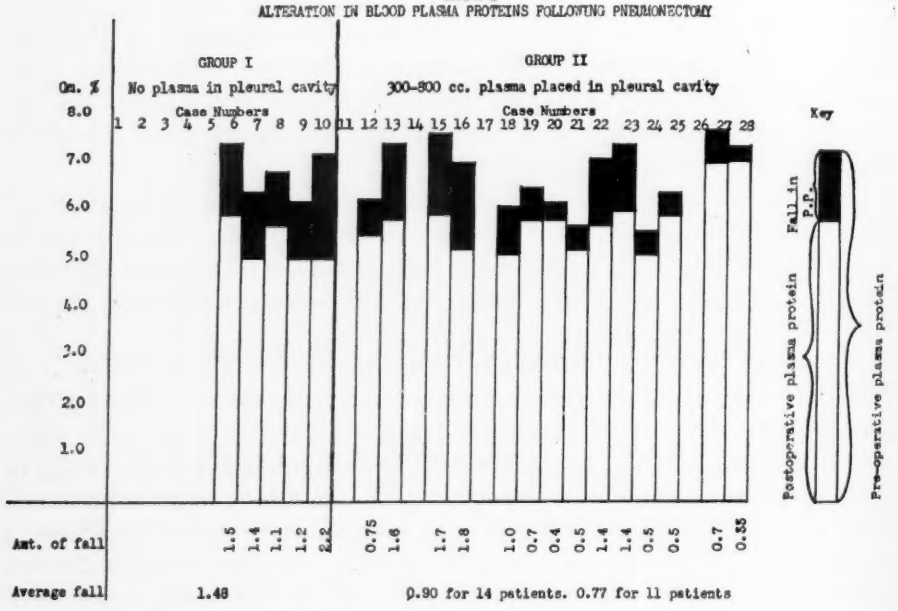
* Patient No. 13 had a tumor of the chest wall two inches in diameter removed in addition to a pneumonectomy. Patient also received 5 Gm. of sulfathiazol in the pleural cavity and drained considerable fluid from the chest wound.

† Patient No. 15 had inadequate replacement by transfusion in addition to receiving 5 Gm. of sulfathiazol in the pleural cavity which produced an increased pleural effusion.

‡ Patient No. 16 received 5 Gm. sulfathiazol in the pleural cavity which resulted in marked pleural effusion—680 cc. being removed to correct for mediastinal shift.

GRAPH I

ALTERATION IN BLOOD PLASMA PROTEINS FOLLOWING PNEUMONECTOMY


GROUP I
No plasma in pleural cavity
GROUP II
300-800 cc. plasma placed in pleural cavity
Gm. %
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
Case Numbers
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
Key
Fall in P.P.
Postoperative plasma protein
Pre-operative plasma protein
Amt. of fall
1.5 1.4 1.1 1.2 2.2 0.75 1.6 1.7 1.8 1.0 0.7 0.4 0.5 1.4 1.4 0.5 0.5 0.7 0.55
Average fall
1.48
0.90 for 14 patients. 0.77 for 11 patients

GRAPH I

the patients falling less than 1 Gm. per cent, which is similar to the findings in the previous study made of this problem. The average fall for the 14 patients who received plasma in the pleural space was 0.90 Gm. per cent. However, if the three patients above mentioned are eliminated the average fall was 0.77 Gm. per cent. In contrast to this, the average fall for the control group was 1.48 Gm. per cent or almost twice that of the 11 treated patients.

The postoperative level as well as the fall in plasma proteins is indicated on Graph I. It is readily seen that a high percentage of the treated patients had only a slight lowering of the plasma proteins and maintained a higher postoperative level than the patients in Group I or the controlled series.

The complications following operation are listed in Table III. The incidence of serious complications and the mortality rate were almost twice as

TABLE III

POSTOPERATIVE COMPLICATIONS FOLLOWING TOTAL PNEUMONECTOMY IN 28 PATIENTS

Group I—Pleural cavity allowed to fill with fluid spontaneously. (10)

Complications:

1. Cardiac failure, 1
2. Sulfonamide anuria, 1
3. Bronchial fistula, 2
4. Empyema, 2
5. Bronchitis and atelectasis, 4
6. Pneumonia, 1

Deaths, 4:

1. Cardiac failure, 1
2. Sulfonamide anuria, 1
3. Infection, 2*

*One death occurred 5 weeks following operation (2.5 weeks after returning home).

Group II—Pleural cavity filled with blood plasma. (18)

Complications:

1. Cardiorespiration failure, 1
2. Pulmonary embolism, 2
3. Pneumonia, 1
4. Bronchial fistula, 1 (temporary—no infection)
5. Empyema, 1

Deaths, 4:

1. Pulmonary embolism, 2
2. Cardiorespiratory failure, 1 (bronchial asthma)
3. Pneumonia, 1 (V. C. 1700 cc. before pneumonectomy)

great in the control group as in the group which received plasma in the pleural space following resection of the lung. Although this series of patients is not large, the discrepancies between the two groups is significant. One of the most striking differences is the high incidence of infection of various types in the control group as compared to the treated patients. Factors influencing this feature are considered in Table IV where the patients are classified according to the method of closure of the bronchus, the use of penicillin, and the use of plasma intrapleurally following operation. The method of closing the bronchial stump has varied somewhat from time to time. However, the first group in which closure was made by two rows of sutures, the proximal being mattress in type, after the method described by Overholt, were not necessarily the first operations performed. Some of the patients in Group II in which closure of the bronchial stump was made with a single row of interrupted sutures over the end of the stump were among the earliest resec-

tions made. A large percentage of the operations in Group II were the most recently performed, using only a single row of sutures for closing the bronchial stump. This fact must be taken into consideration in interpreting the low incidence of complications in this group.

TABLE IV

RESULTS FOLLOWING TOTAL PNEUMONECTOMY IN 28 PATIENTS CLASSIFIED ACCORDING TO TYPE OF BRONCHIAL CLOSURE AND THE USE OF PLASMA AND PENICILLIN IN THE PLEURAL CAVITY

		Complications						
	No. of Cases	Atelectasis	Pneu.	Emp.	Fist.	Pul. Emb.	Card. Fail.	Deaths
I. Closure of bronchial stump with two rows of sutures								
a. No plasma in pleural cavity	7	2	1	3	2	0	1	4 (1—Fistula & emp.; 1—Card. failure; 1—Empyema and pericarditis; 1—Sulfonamide anuria)
b. 300 to 600 cc. plasma in pleural cavity	5	0	0	1	1	1	0	1—Pulmonary embolism
Total	12	2	1	4	3	1	1	5
II. Closure of bronchial stump with one row of sutures								
a. No plasma in pleural cavity	3	1	1	0	0	0	0	0
b. 500 to 800 cc. plasma in pleural cavity	4	0	0	0	0	1	0	1—Pulmonary embolism
c. 550 to 1000 cc. plasma and 200,000 U. penicillin in pleural cavity	9	0	1	0	0	0	1	1 (Cardiorespiratory failure (bronchial asthma)); 1 (Bronchial pneu. (V.C. 1700 cc. preop.)
Total	16	1	1	0	0	1	1	3

The highest incidence of complications and greatest mortality was found in Group Ia where two rows of sutures were used for closing the bronchus. When plasma was placed in the pleural space in addition to the above method of bronchial closure the incidence of complications was considerably lowered (see Ia and b). The lowest incidence of complications was obtained in Group II-C where the bronchial stump was closed with a single row of interrupted sutures and the patient received plasma and penicillin intrapleurally following operation. Of the nine patients, one had bronchial asthma, and died of pulmonary insufficiency following operation. Another patient had a vital capacity of only 1,700 cc. before operation and died on the fifth postoperative day of what appeared to be bronchial pneumonia. This patient was receiving 120,000 to 160,000 units of penicillin daily in addition to 200,000 units in the pleural cavity. There was no infection on the side of operation. There were no other complications in this group.

A striking difference in the incidence of postoperative empyema and bronchial fistula was seen between the two methods of bronchial closure.

Of the 12 cases closed by the two row suture technic, four developed an empyema, three of which had a bronchial pleural fistula. In contrast with this, none of 16 patients whose bronchial stump was closed by the single row suture technic developed either an empyema or fistula following operation. The remaining complication, namely, pulmonary embolism, was observed twice in the entire series of 28 cases, and was fatal in each patient. One occurred in each type of bronchial closure. The etiology for this complication was not demonstrable.

Discussion.—In a clinical study such as this, where a number of variables are unavoidable, it is difficult to accurately interpret the influence of the various factors on the results obtained. In addition to the data presented, one other factor was present in all patients except Nos. 1 and 2, namely, oral or intravenous administration of sulfonamides before and following pneumonectomy. In view of the fact that this therapy was used practically throughout the series, it is probable that it did not play a rôle in the discrepancy of results between the control and treated groups of patients.

The results of the blood studies, including the plasma proteins, reveal that for the most part the blood loss during and following operation was not completely replaced by transfusion although it was our intention to do so; further that the plasma protein level could not be predicated by the blood count and hemoglobin values.

Although the operative wound practically always healed by primary intention (exception—Case 13), the incidence of pneumonia, bronchitis, atelectasis, and empyema were twice as frequent in the control group of patients as in the group in which the pleural space was filled with plasma. Just how much the increased lowering of the plasma proteins in the control group contributed to the increased incidence of infection is difficult to say. In view of the fact, as has been pointed out earlier, that infection and delayed wound healing showed a striking parallel to subnormal blood plasma proteins in experimental studies, it is at least suggestive that a relationship existed between the two.

At postmortem examination on two patients expiring three and five days after pneumonectomy (Nos. 26 and 28) the bronchial stumps were securely closed and covered by a very firm layer of fibrin. This fibrin also extended into the fluid of the pleural cavity, the major portion of the latter having been placed there at the end of operation. It would seem reasonable to believe that a continual bathing of the region of the bronchial stump with plasma might contribute to the maintenance of its closure following surgery. In addition, the plasma as a vehicle for the penicillin simultaneously placed in the pleural cavity would carry the penicillin to all parts of the cavity in a concentration sufficient to ward off active infection resulting from unavoidable contamination at the time of operation. The results in the nine patients in which this was done would bear out this reasoning since in no patient was there infection in the pleural cavity following the removal of the lung on that side. This was true in spite of the fact that in one patient death due to bronchial pneumonia occurred five days after surgery (Case 28).

SUMMARY AND CONCLUSIONS

The influence of filling the pleural space with plasma following total pneumonectomy was studied in 18 patients and the results compared with those in ten control patients.

Blood studies made before and after operation showed less lowering of the plasma proteins in the treated group (average of 0.77 Gm. per cent as compared to 1.48 Gm. per cent in the control patients). More significantly, the blood proteins in the treated patients were in general maintained at a higher level than those of the control group (5.8 Gm. per cent as compared to 5.3 Gm. per cent).

The incidence of complications following operation, including empyema, bronchial fistula, bronchitis, atelectasis and pneumonia, was much less in the group of patients whose pleural space was filled with plasma, being approximately 50 per cent of that of the control group.

The influence of subnormal blood and tissue proteins on wound healing and the development of infections is discussed.

REFERENCES

1 Graham, E. A., and Singer, J. J.: Successful Removal of Entire Lung for Carcinoma of Bronchus. J. A. M. A., **101**, 1371, October 28, 1933.

2 Rienhoff, Wm. F., Jr.: The Present Status of the Surgical Treatment of Primary Carcinoma of the Lung. J. A. M. A., **126**, 1123, December 30, 1944.

3 Longacre, J. J., and Johansmann, Ralph: An Experimental Study of the Fate of the Remaining Lung Following Total Pneumonectomy. J. Thoracic Surg., **10**, 131, 1940.

4 Thompson, W. D., Ravdin, I. S., and Frank, I. L.: Effect of Hypoproteinemia on Wound Disruption. Arch. Surg., **36**, 500, 1938.

5 Thompson, W. D., Ravdin, I. S., Rhodes, J. E., and Frank, I. L.: Use of Lyphile Plasma in Correction of Hypoproteinemia and Prevention of Wound Disruption. Arch. Surg., **36**, 509, 1938.

6 Cannon, Paul R.: Protein Metabolism and Acquired Immunity. J. Am. Dietetic Assoc., **20**, 77, 1944.

7 Cannon, Paul R., Wissler, Robert R., Woolridge, M. S., and Benditt, Earl P.: The Relationship of Protein Deficiency to Surgical Infection. ANNALS OF SURGERY, **120**, 514, 1944.

8 Adams, W. E., and Thornton, T. F., Jr.: The Use of Plasma for Filling the Pleural Space after Loss of Varying Amounts of Lung. Surgery, **15**, 521, 1944.

9 Thornton, T. F., Jr., Adams, W. E., and Schafer, P. W.: Hypoproteinemia in Thoracic Surgery. Surg., Gynec. & Obst., **79**, 368, 1944.

10 Peters, John P., and Van Slyke, Donald D.: Quantitative Clinical Chemistry. P. 516. Baltimore, Maryland: The Williams & Wilkins Co., 1932.

11 Thomas, Louis., Adams, D. E., and Thornton, T. F., Jr.: Alterations of the Blood Following Intrathoracic Operations: A Clinical Study. J. Thoracic Surg., in press.

CHRONIC LEPTOMENINGEAL THICKENING FOLLOWING TREATMENT OF MENINGITIS WITH SULFA-DRUGS

PERCIVAL BAILEY, M.D., PH.D.

CHICAGO, ILL.

FROM THE DEPARTMENT OF NEUROLOGY AND NEUROLOGICAL SURGERY, UNIVERSITY OF ILLINOIS, AT THE ILLINOIS NEUROPSYCHIATRIC INSTITUTE, CHICAGO, ILL.

SINCE THE INITIATION of serum therapy of meningococcic meningitis various neurologic defects have been recorded as sequels to otherwise successful treatment of the infection. Among these may be mentioned infantile hemiplegia or diplegia, paraplegia in adults, deafness and deaf mutism, and aphasic troubles, but the most common late complication is chronic hydrocephalus. As the infection is overcome the purulent exudate is organized by proliferation of fibroblasts which occlude the narrow pathways in the leptomeninx and obstruct the circulation of the cerebrospinal fluid. It might have been expected that the same train of events would follow the suppression of a suppurative meningitis by sulfa-drugs or penicillin. Lately we have observed numerous examples.

CASE REPORTS

Case 1.—J. H., a male, age 16, was admitted, November 14, 1944, because of repeated convulsions.

In August he developed an earache. On August 29 the right ear drained spontaneously. Sulphathiazole was administered on August 30 and on August 31 a right mastoidectomy was performed. On September 7 he had a high fever and stiff neck with severe headache. A lumbar puncture secured cloudy fluid containing 1523 leukocytes per cu. mm. and numerous gram-positive cocci. Cultures of the fluid remained sterile. On October 4 the spinal fluid contained 1240 leukocytes but, again, no growth was obtained from the fluid. Aside from continuous administration of sulphadiazine 75,000 units of penicillin were given intraspinally in nine separate doses of 5,000–10,000 units between September 7 and October 25. By October 12 his temperature was normal but a week later he became suddenly much worse, was irrational and uncoöperative and his temperature rose to 104° F. On October 23 a lumbar puncture obtained cloudy fluid with 29,500 cells. He began to have convulsions and was admitted to the Institute.

He was irrational with a temperature of 103° F. The right pupil was larger; there was a ptosis of the left upper eyelid and a right facial paralysis. His neck was stiff.

He was given sedatives to quiet him and 100,000 units of penicillin intramuscularly, but his temperature rose steadily and he expired the following morning.

Necropsy disclosed a left acute otitis media, an early interstitial pneumonia, a partially healed right mastoidectomy wound, and passive congestion of the spleen and adrenal glands. *Alpha* streptococci were grown from the base of the brain and *gamma* streptococci from the left middle ear.

On external inspection of the brain one saw a milky thickening of the leptomeninx over the base and extending up the lateral fissures toward the vertex. The ventricles were not dilated but the ependyma was juicy, yellowish and cloudy; the left temporal horn appeared to contain a small amount of pus.

Microscopic examination disclosed here and there in the leptomeninx small abscesses and clumps of macrophages filled with débris. Aside from the small abscesses the predominant infiltrative cells in the leptomeninx were lymphocytes and plasma cells with an

occasional polymorphonuclear leukocyte (Fig. 1). The most striking feature, however, was the unusual proliferation of fibroblasts with the production of vast numbers of connective tissue fibrils.

The ventricles were the seat of an acute purulent infection with an inflammatory exudate consisting predominantly of polymorphonuclear leukocytes.

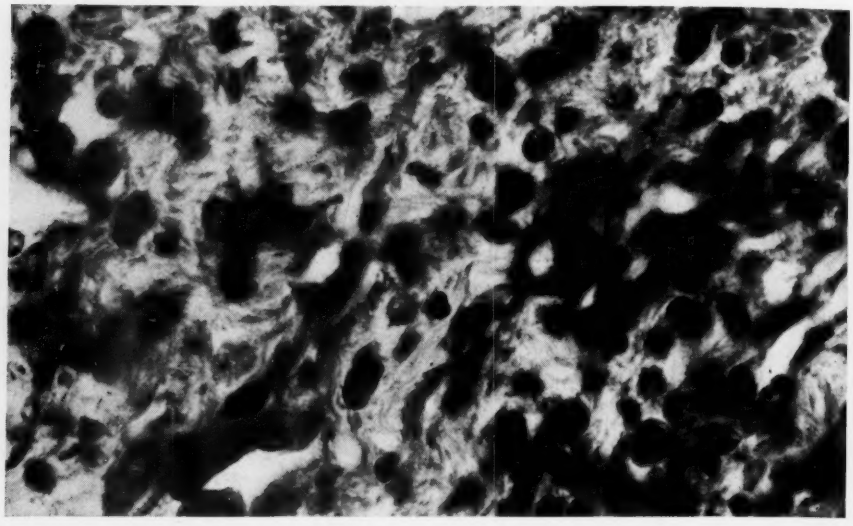


FIG. 1.—Case 1: Unusual proliferation of connective tissue fibrils forming a network in the meshes of which are entangled lymphocytes, plasma cells and an occasional polymorphonuclear leukocyte.

COMMENT: The meningitis seemed to be well on the way to healing. The sudden increase of symptoms leading to death would seem to be due to an extension of the infection to the ventricular system.

Case 2.—L. di J., a female child, age 11, was admitted November 18, 1942. Born normally, she had been well, except for measles at the age of seven, until August 1942 when she developed a severe headache. Because she had a fever she was given sulphathiazole for some time, how much is not known, and improved somewhat but later became worse and was taken to an hospital where a lumbar puncture was made on October 17. The initial pressure was 115 mm. of water. There was an increased cell count, mainly polymorphonuclear leukocytes, the actual count being unknown. On November 5 another puncture is said to have found increased pressure, the fluid was turbid and contained 9,000 cells, 80 per cent polymorphonuclear leukocytes. Cultures of the fluid were negative. She was then given sulphadiazine, how much is unknown, and her fever returned to normal but she became unresponsive.

When admitted to the Institute her temperature was 101° F. by rectum but promptly dropped to 99.6° and thereafter fluctuated around 100° until near her death when it reached 104°. She was emaciated and dehydrated. The leukocyte count in the blood was 8,250. She could be roused with difficulty to respond with a feeble cry and to answer questions briefly. Her neck was slightly stiff. There was a bilateral Kernig sign and bilateral Babinski signs. The ear drums were normal. The optic disks were slightly blurred but not elevateed. Both external rectus muscles were paretic.

A lumbar puncture obtained slightly turbid fluid with a count of 500, mainly polymorphonuclear leukocytes. Cultures of the fluid were negative. On December 8 there were still 600 cells in the fluid. Cultures were again negative and injected guinea-

pigs remained healthy. Wassermann tests were negative on the blood. Mantoux test was negative.

On December 11 a ventriculogram was made and disclosed only generalized dilatation of the ventricles.

She became slowly more stuporous and expired January 31, 1943. Necropsy disclosed a patchy bronchopneumonia, cloudy swelling of the kidneys, liver and adrenal glands, hemorrhagic cystitis and fatty degeneration of the liver. *Gamma* streptococci were grown from the leptomeninges.

The brain was of normal size but the markings of its inferior surface were obscured by a whitish thickening of the leptomeninx of the basilar and posterior cisterns. This pathologic alteration did not appear to extend to the lateral or interhemispheric fissures. There was a moderate internal hydrocephalus. The interventricular foramina and the aqueduct were not obstructed.

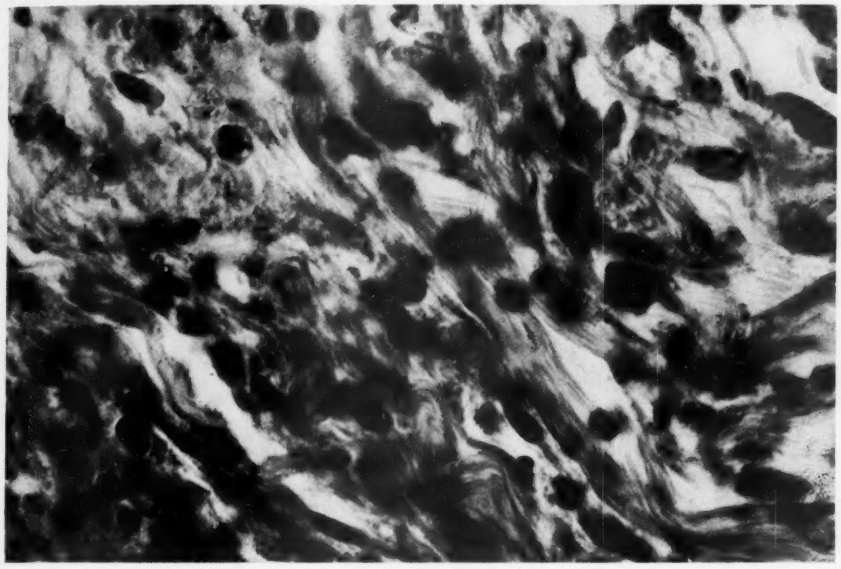


FIG. 2.—Case 2: Leptomeningeal infiltration containing scattered polymorphonuclear leukocytes but great numbers of flourishing fibroblasts.

Microscopic preparations revealed the thickening of the leptomeninx to be due to a marked fibroblastic proliferation from the walls of the numerous vessels. In addition, there were foci of chronic inflammatory reaction, consisting mainly of lymphocytes and plasma cells but with numerous polymorphonuclear leukocytes. No tubercle bacilli and no other pathogenic organisms were found. The fibroblasts were flourishing, forming broad bands of fibrils (Fig. 2).

COMMENT: Again, the infection had been checked but not destroyed, and the thickening of the leptomeninx had already begun to produce an hydrocephalus.

Case 3.—D. A. H., a male child, age four months, was admitted August 10, 1943.

Of normal birth, he was breast-fed and well until he was one month old, at which time he developed a high fever. A diagnosis of meningitis was made and the child was treated with sulfanilamide. On July 12 his temperature was 102° F., his neck was stiff and the fontanel bulging. Lumbar puncture obtained cloudy fluid, with 12,735 leukocytes and 14 mg. per cent of sulfanilamide. He was then given 30 cc. antimeningococcus serum

intravenously and sulfadiazine was begun. On July 14 his sulfadiazine level in the blood was 41.1 mg. per cent; in the ventricular fluid 63 mg. per cent. On July 26 the spinal fluid contained 1,673 cells. Cultures of the spinal fluid on several occasions were always negative. His temperature subsided to normal by September 25, but he remained stuporous.

When admitted, the child's head was retracted and measured 49 cm. in circumference. The anterior fontanel was widely open and bulging. The cranial sutures were separated. He was emaciated and dehydrated. His temperature was 103° F. on admission but subsided promptly to around 99°. The ear drums were normal.

FIG. 3.—Case 3: Vast tangle of robust fibroblasts with an occasional macrophage.

A roentgenogram of the skull showed dilatation of the sutures. On August 24 the lateral ventricle was punctured and air was injected, demonstrating a wide general dilatation of the ventricular system. The ventricular fluid contained seven lymphocytes per cubic centimeter and nothing was cultured from it. Following this procedure the temperature rose to 106° F. but promptly fell and remained around 99° until the child's death on October 20.

Necropsy disclosed an early bronchopneumonia. No organisms were grown from the brain or meninges.

The cerebral hemispheres were enormously dilated and the cortex greatly thinned. The interventricular foramina and the aqueduct were widely dilated. There was a large opening through the septum pellucidum. There was a marked whitish thickening of the leptomeninges over the entire base of the brain, extending upward along the lateral and interhemispheric fissures but less evident over the vertex.

On microscopic examination, the thickening was found to be caused principally by an enormous proliferation of fibroblasts and capillary blood vessels (Fig. 3). A great many macrophages, containing blood pigment, were present but only a few inflammatory cells, mostly lymphocytes and plasma cells. There were no tubercles and no giant cells. Tubercle bacilli were not found. Within the parenchyma of the brain only the changes due to the hydrocephalus were found.

COMMENT: In this case the infection seems to have been eradicated but the hydrocephalus steadily increased.

Case 4.—R. S., male, age 15, was admitted January 6, 1945. He was well until December 6, 1944, when he complained of pain in the back. On December 7 he had a chill and headache. December 10 he was taken to an hospital where he was found to have a fever of 102.8° F. and a stiff neck. The spinal fluid was cloudy and contained 10,000 leukocytes per cu. mm. Cultures of the fluid remained negative after 48 hours. He was given sulfadiazine, five to six grains per day, and 200,000 units of penicillin within the next 48 hours. His temperature rose to 105°. On December 13 he was given 100,000 units of penicillin, intraspinally, in two doses of 50,000 each. The sulfadiazine was changed to sulfathiazole, 30 grains four times daily. Penicillin was again given; by December 16, 300,000 units had been given. On that day he had several convulsions. December 17 a transfusion of 400 cc. blood was given and, on December 21, another. On December 23 the patient had difficulty in moving his legs. December 25, no

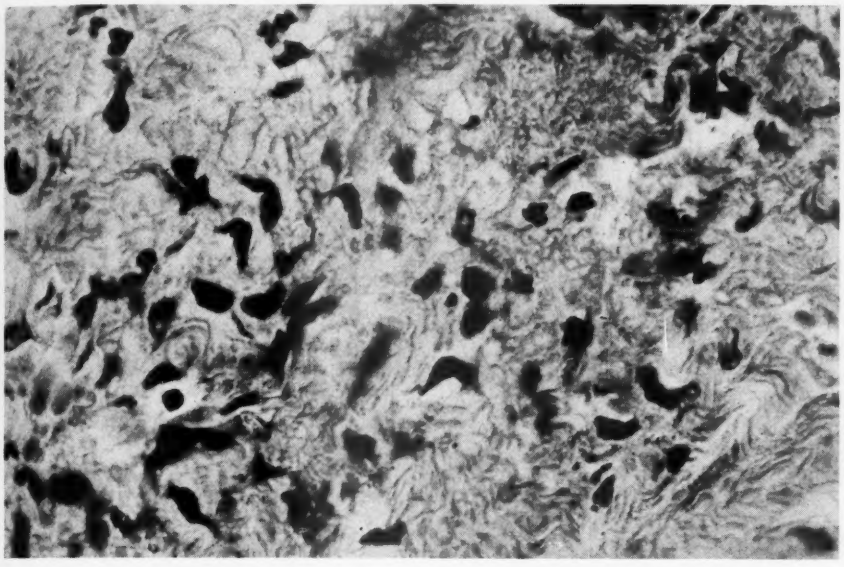


FIG. 4.—Case 4: Leptomeninx consists of a dense scar of collagenic connective tissue.

fluid could be obtained by spinal puncture; both legs were now paralyzed. On January 6 he was transferred to the Institute.

His temperature was normal. He had a completely flaccid paraplegia, with loss of both tendon and superficial reflexes and a positive Beevor's sign. There was anesthesia to all forms of sensation over the sacral dermatomes and hypesthesia up to D_{10}. He was incontinent of urine.

Lumbar puncture was made at various levels up to D_8 but no fluid was obtained. On January 9 a laminectomy was performed at $D_{7\,8\,9}$ under local anesthesia. The dura mater was lightly adherent to the arachnoid membrane. The subarachnoid space was completely obliterated and the spinal veins thrombosed. A biopsy was made of the greatly thickened leptomeninx.

The wound healed promptly and he was discharged, condition unchanged, January 25, 1945.

Examination showed that the leptomeninx had been transformed into a dense scar of collagenic tissue. Inflammatory cells were entirely absent (Fig. 4).

COMMENT: This case demonstrates the end-stage of an inflammatory exudate which predominated in the spinal region.

SUMMARY

In all of these cases the course of events was much the same: an acute purulent infection which was controlled or cured by administration of sulfa-drugs or penicillin but the condition went on to death or some serious sequel. The disabling sequels are largely the result of the fact that these drugs exert no restraining influence on the fibroblasts which proliferate enthusiastically in their attempts to organize the exudate. The result is the transformation of the leptomeninx into a dense scar through which the cerebrospinal fluid cannot circulate and the contraction of which may constrict blood vessels and pathways essential to proper functioning of the nervous system.

It is not suggested that these drugs be not used in the treatment of suppurative leptomeningitis but a plea is made for early diagnosis and intensive therapy before a massive exudate has occurred and it is suggested that in any case the prognosis should be very guarded.

RADICAL RESECTIONS OF ADVANCED INTRA-ABDOMINAL CANCER

SUMMARY OF RESULTS IN 100 PATIENTS*

ALEXANDER BRUNSCHWIG, M.D.

CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF CHICAGO, CHICAGO, ILL.

IN RECENT YEARS, advances in the supportive treatment for surgical patients have reduced the risks attendant upon major operative procedures. These supportive measures include the prevention and treatment of shock by liberal use of blood and plasma, especially the former, refinements in anesthesia, especially the introduction of continuous spinal, greater appreciation of the importance of fluid and electrolyte balance and the general nutritional status, and the introduction of chemotherapy, especially for pulmonary and urinary complications.

Measures for the reduction of mortality also permit of the extension of operative surgery in situations which although regarded as technically possible, in the past, were considered beyond feasibility because of the belief that the patients would not survive.

During the past few years the writer has performed radical or massive resections in 100 patients with abdominal malignant tumors, which, by the usual criteria, were in the advanced stage. The literature includes a number of reports of very radical resections of abdominal cancer carried out in individual or small groups of patients but insofar as could be determined there have been no published studies of the possible benefits of such surgery in a significant series. Immediate survivals alone in isolated instances, interesting as these might be, would not justify advocacy of a general extension of operative attack upon advanced intra-abdominal cancer when effective palliation might be envisaged by the more conservative short-circuiting operations if obstructions of one type or another existed.

Since no two patients present identical situations comparative studies are impossible; furthermore, such studies cannot include "controls" as in the case of laboratory experiments upon animals. Moreover, "five-year survivals" in patients with advanced abdominal cancer, as a rule, can hardly be envisaged. The results, therefore, must be expressed in terms of palliation received. This is difficult to evaluate properly since a surprising degree of palliation may obtain by conservative measures. For example, not of the least importance, is an interested and encouraging attitude on the part of the attending physician, with judicial use of sedation. Great emphasis on maintaining a good nutritional state in the patient is also of paramount importance. Relief from pain and

* The records of these case histories were facilitated by the O. C. Miller Fund for Cancer Research of the University of Chicago.

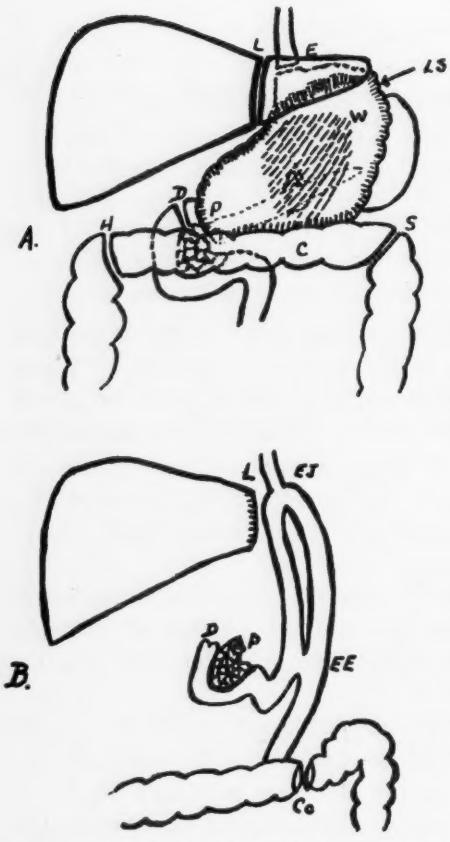


FIG. 1A.—Case 1 (339809): (A) Diagram showing levels of transection: (L) base of left lobe of liver; (E) esophagocardiac junction; (D) pylorus; (H) hepatic flexure; (S) splenic flexure; (P) neck of pancreas; (LS) large lymphosarcoma replacing practically all of stomach; (W) abdominal wall musculature and deep fascia invaded by tumor and excised *en masse* with the neoplasm.
(B) Situation at the close of the operation; (L) stump of liver after resection of left lobe; (EJ) esophagojejunostomy; (EE) entero-enterostomy; (D) invaginated duodenal stump; (P) transected neck of pancreas; (CO) colostomy, hepatic to splenic flexures.

adequate regulation of nutrition, may result in remarkable gain in weight. Relief of obstructions alone, even in advanced stages of abdominal cancer may on occasion afford appreciable palliation for an unanticipated period. Those who have followed carefully patients with slowly advancing cancer are also aware of the powers of suggestion and psychotherapy in obtaining for certain periods, at least a sense of well-being.

The patients considered in this series presented varying types of neoplasms with varying degrees of metastases and local extensions. Thus, the series of operations is an heterogeneous one indeed, and in almost every instance was not a standard procedure but one devised to the situations encountered. Limiting consideration to the endeavors of a single operator serves to control such factors as minutiae of technic, surgical judgment, manual dexterity, *etc.*

A definition of what constitutes radical or massive resections of advanced abdominal cancer is difficult to formulate. The following are examples:

CASE REPORTS

Case 1.—E. B. (No. 339809). Male, age 28.

Resection of large round cell sarcoma primary in and practically replacing the entire stomach with spread to neighboring organs and tissues. The entire stomach, half of left lobe of liver, body and tail of pancreas, spleen, left adrenal, transverse colon, entire omentum and abdominal wall in the left upper quadrant were excised *en masse;* double-barrel colostomy, hepatic end of ascending colon to splenic end of descending colon through stab wound to one side of midline incision (Fig. 1).

Result: Survival for over two months with ability to relish food eaten and appreciable relief from pain. Died of rapidly progressing generalized sarcomatosis, the period of deterioration lasted for only two weeks.

Case 2.—F. W. (No. 328218). Male, age 68.

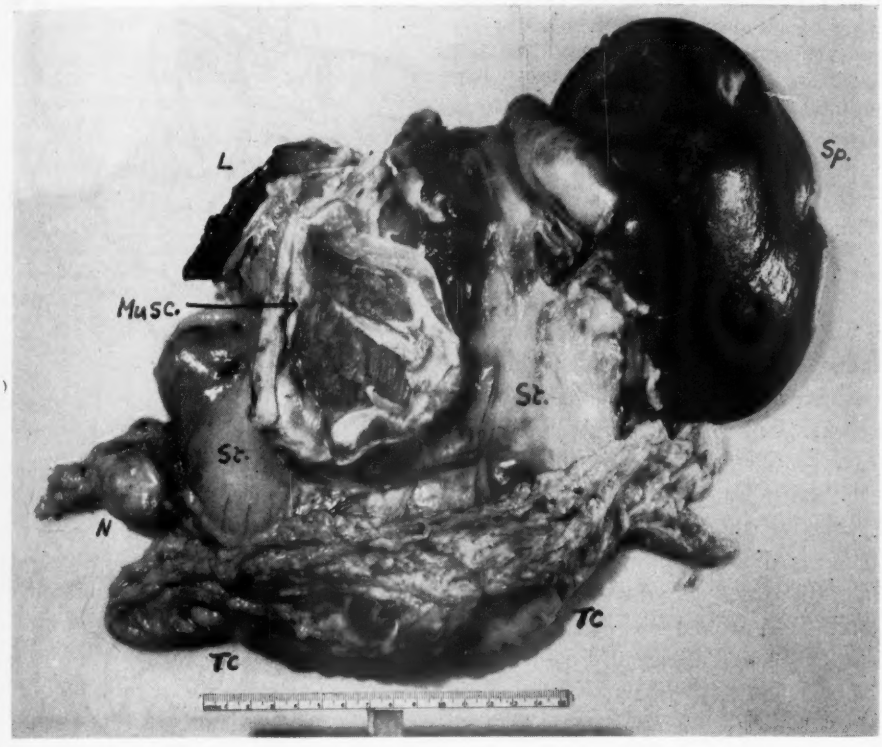
Resection *en masse* of entire stomach, entire pancreas, entire duodenum, left adrenal, spleen and entire omentum for carcinoma of the body of the pancreas directly invading the posterior wall of the stomach, with metastases to nodes along lesser curvature and in greater omentum.

Result: Survived three and one-half months. Relief from pain and jaundice for two and one-half months. (Previously reported in greater detail.[1])

Case 3.—P. H. (319547). Male, age 49.

Resection *en masse* of entire sigmoid colon, dome of urinary bladder, terminal half of left spermatic cord, abdominal wall (except skin and superficial fascia) in left lower

FIG. 1 (Cont'd)



C

FIG. 1C.—Case 1 (339809): Photograph of surgical specimen consisting of (St) entire stomach almost completely replaced by round cell sarcoma primary in fundic portion; (L) half of left lobe of liver invaded by neoplasm; (Sp) spleen; (TC) entire transverse colon and contracted omentum; (N) large metastatic lymph node from over head of pancreas; (Musc.) musculature, deep fascia and anterior parietal peritoneum from left upper quadrant of anterior abdominal wall invaded by tumor. The body and tail of pancreas, and left adrenal gland were also resected but are not seen here as they are on the reverse aspect of the specimen. Operation completed by esophagojejunostomy, jejujejunostomy and double-barrel colostomy (hepatic end of ascending colon to splenic end of descending colon). Duration of operation: 3 hours 35 minutes. Continuous spinal anesthesia. Received 2,400 cc. blood, 500 cc. plasma and 3,300 cc. saline intravenously. At termination of operation there was no gross evidence of neoplasm remaining in the abdomen. Satisfactory convalescence, received palliation for over 2 months, the patient succumbed from rapidly developing generalized sarcomatosis that proved resistant to irradiation. Period of deterioration lasted 2 weeks.

quadrant, 30 cm. of ileum with corresponding mesentery extending up to origin of superior mesenteric artery and including metastatic nodes palpable up to this artery for carcinoma of sigmoid invading loop of ileum to production of ileocolic fistula, also invading dome of urinary bladder, intra-abdominal portion of left spermatic cord and abdominal wall in left lower quadrant. Side-to-side entero-enterostomy, closure of remaining urinary bladder, double-barrel colostomy. Latter subsequently closed.

Result: Survived 14 months; died of recurrences. Returned to heavy physical work (truck driver) for six months.

Case 4.—S. P. (No. 264586). Male, age 68.

Resection *en masse* of gallbladder, surrounding liver parenchyma, all extrahepatic bile ducts except for small terminal stump of common duct, and portion of head of pancreas, for carcinoma primary in extrahepatic bile ducts. T-tube inserted between right hepatic duct sinus in liver and stump of common duct at duodenum. The left hepatic duct stump was cannulated with urethral catheter; the latter came away in two months and sinus closed. No discharge of bile about T-tube.

Result: Icterus cleared, relieved of pain. Survived one year, returned to full-time normal occupation (accountant) for six months. Died of recurrences.

Space does not permit of the detailed description of each of the 100 patients in the series considered in this report. The results are classified into four groups as follows:

GROUP IV.—Thirty-four patients: Operative mortality. In this study patients dying within four weeks of operation are classified as operative deaths regardless of other possible causes. Some apparently died of carcinoma but this did not alter their classification in view of the time of survival after operation. The causes of death are summarized in Table I.

GROUP III: Fourteen patients. During the period of survival palliation was minimal or did not obtain. At this writing three are alive, averaging four months since operation. Of the 11 patients who have died, all of carcinoma, the average postoperative survival was two and seven-tenths months. Two lived five, and five and five-tenths months, respectively; one, four months; two, three months, respectively, and six, one to two months.

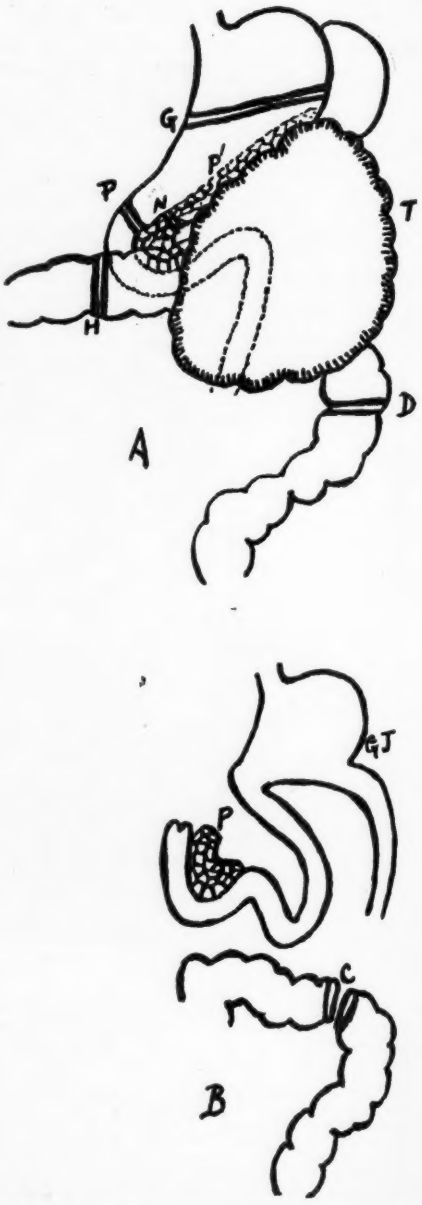


FIG. 2A.—Case 332950: Diagram of operation showing levels of transection: (G) division of stomach; (P) pylorus; (N) neck of pancreas; (P') body of pancreas excised with specimen; (N) neck of pancreas transected; (H) transverse colon transected near hepatic flexure; (D) descending colon near junction with splenic flexure.

(B) Situation at close of operation; (GJ) gastrojejunostomy; (P) transected neck of pancreas; (C) colostomy, hepatic flexure to upper portion of splenic segment of colon.

GROUP II-a: Twenty-three patients. This group includes patients who survived over one month to 14 months, received varying degrees of palliation

which, however, it is felt was sufficient to have justified operation and who since have died of carcinoma. The average period of survival was five and eight-tenths months. Five patients survived 10, 11, 12, 14 and 14 months, respectively. Three patients survived six to seven months.

TABLE I

CAUSE OF DEATH IN 34 PATIENTS SUBJECTED TO RADICAL RESECTION OF ADVANCED ABDOMINAL CANCER

Peritonitis—No gross evidence of perforations	6
Peritonitis—Ischemic perforations or leakage of anastomosis (1 case)	6
Pulmonary complications (pneumonia)	6
Accidental resection of segment of hepatic artery	2
Accidental ligation of superior mesenteric vein	1
Thromboses, intrahepatic radicals of portal vein	2
Uremia	1
"Exhaustion." Patients markedly debilitated by carcinomatosis, no specific cause of death revealed at necropsy	2
Acute gastric dilatation	1
Multiple thrombi splanchnic vessels and ischemic necrosis, gastric stump	1
Acute adrenal insufficiency	1
Necropsy not obtained	5
Total	34

GROUP II-b: Twelve patients. This group comprises the patients who have survived operation at least two months, have received sufficient palliation to have justified operation and who are living at this writing. Four who have survived operation an average of four and two-tenths months have clinical evidence of advancing disease but are considered to be in better condition than before operation. Four are living, well, and returned to usual full-time occupation, 12, 11, eight and eight months after operation, respectively. Four have been operated upon two to three months previous to this report, and are well.

GROUP I-a: Twelve patients. Prolonged palliation, survival at least 18 months, returned to usual occupation full-time. No evidence of carcinoma.

GROUP I-b: Five patients, prolonged palliation but eventually died of recurrent carcinoma.

The question might be raised that patients in Groups I-a and I-b include lesions which are not "advanced" and, thus, received more conservative operations than those in the other groups. That this was not the case is shown in Table II which summarizes the extent of the neoplasms and the operative procedures.

Ten patients are living and well an average of four years after operation (Group I-a). Five patients have died of recurrent and metastatic carcinoma, having survived operation for an average of two and one-half years (Group I-b).

Included in Group I-a are two patients who were subjected to multiple stage radical resections of the pelvic colon in the face of clinical evidence of recurrent and metastatic carcinoma of the uterus following irradiation therapy. In both instances the primary growths (biopsied) were of such size as to leave the impression that their eradication by irradiation would probably not be successful. When readmitted they presented obstruction of the colon and

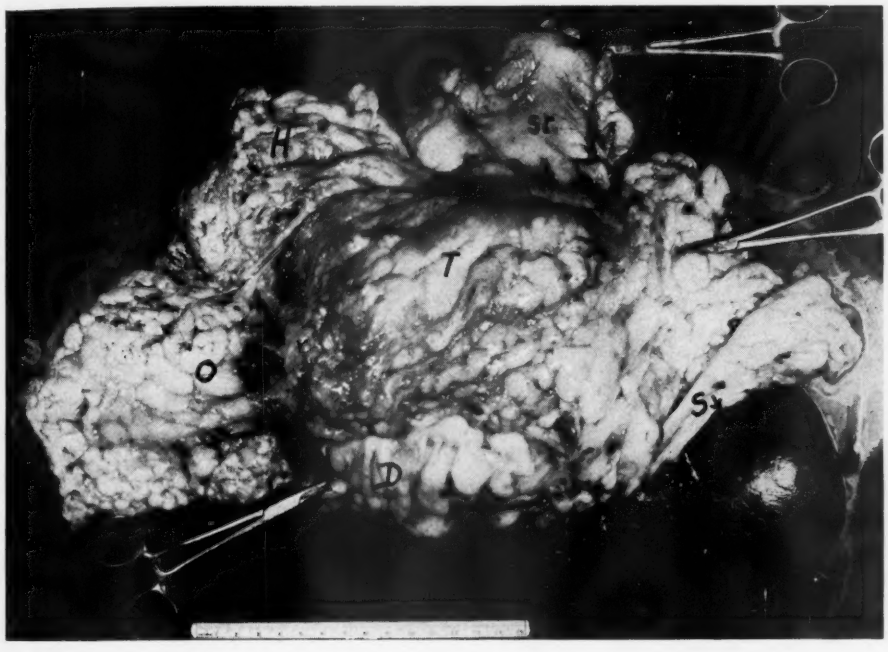
TABLE II

SUMMARY OF OPERATIVE PROCEDURES AND RESULTS IN PATIENTS IN GROUPS Ia AND Ib DESCRIBED IN TEXT

Patient and Hosp. No.	Findings and Procedure	Result
GROUP 1-a.		
1. E. C. (134969)	Carcinoma first loop of jejunum extending upward in mesentery, into body of pancreas and posterior to this into retroperitoneal tissues. Resection of 10 cm. of upper loop of jejunum with involved mesentery, distal third of body of pancreas and upper retroperitoneal extensions. End-to-end jejujejunostomy and gastrojejunostomy distal to this.	Well 10 yrs.
2. R. H. (186022)	Large ulcerating carcinoma second portion of duodenum invading adjacent pancreas. Resection of inner curvature of second portion of duodenum and subjacent pancreatic tissue.	Well 7 years, 4 months
3. N. A. (261816)	Carcinoma of lower third of stomach directly invading left lobe of liver, one detached metastasis in left lobe. Resection of lower three-fifths of stomach and left lobe of liver *en masse*.	Well 4 years, 2 months
4. R. Z. (263077)	Carcinoma hepatic flexure with invasion of capsule of right lobe of liver and invasion of loop of ileum 20 cm. proximal to cecum. Right hemicolectomy with resection of lower 30 cm of ileum, all corresponding mesenteries and involved portion of right lobe of liver 10 x 6 x 4 cm. Ileotransverse colectomy.	Well 3 years, 8 months
5. H. S. (27336)	Large fungating carcinoma of fundus of stomach with extensive lymph node metastases in gastrohepatic ligament and throughout most of omentum. Total gastrectomy and omentectomy, splenectomy. Transection of esophagus about 1 cm. beyond gross limits of tumor.	Well 3 years, 6 months
6. J. C. (287119)	Large carcinoma of transverse colon invading stomach above and fungating through abdominal wall in periumbilical region. Resection *en masse* of transverse and ascending colon, lower 15 cm. of ileum, segment of abdominal wall 8 x 6 cm., including skin and umbilicus, lower half of stomach. Ileosplenic flexure colostomy. Pólya gastrojejunostomy; repair defect in abdominal wall (Fig. 4).	Well 3 years, 6 months
7. G. J. (142751)	Resection of lower half of head of pancreas, lower half of duodenum, regional lymph node metastases, double fist-size spindle cell sarcoma of third portion of duodenum. During operation superior mesenteric vessels were dissected free from tumor. Duodenojejunostomy.	Well 3 years
8. L. L. (284407)	Massive carcinoma of left adrenal invading diaphragm above, musculature of posterior abdominal wall left side, surrounding upper pole left kidney and apparently invading body and tail of pancreas. Resection of tumor, left kidney, body and tail of pancreas, spleen, portion of left diaphragm and muscle and fascia of left posterior abdominal wall.	Well 3 years
9. N. G. (2648)	One-stage pancreatoduodenectomy for large carcinoma of ampulla of Vater with regional lymph node metastases resected including a large node high in the porta hepatis.	Well 2½ years
10. L. R. (332950)	Large carcinoma left transverse colon with invasion of lower stomach and body of pancreas. Resection *en masse* of lower half of stomach, spleen, body and tail of pancreas, left three-fourths of transverse colon, descending colon and entire omentum. Double-barrel colostomy—hepatic flexure to sigmoid in left abdominal wall; subsequent closure of the latter (Fig. 2).	Well 1 year, 7 months
GROUP 1-b		
1. J. L. (233821)	Massive islet cell carcinoma of body of pancreas, 15 cm. in diameter, invading stomach and segment of upper jejunum. Resection of body of pancreas, tumor, spleen, portions of gastric and jejunal wall invaded by tumor.	Lived 3 years, 11 mos. Died of complications of celiotomy performed for resection of metastases
2. R. W. (287625)	One-stage pancreatoduodenectomy for large carcinoma termination of common bile duct.	Lived 2 years, 2 mos. Died—recurrences
3. C. B. (255477)	Multiple resections of right colon and portions of abdominal wall for recurring carcinoma. Well and active during intervals between operations.	Lived 2 years, 6 mos. Died coronary occlusion 3 weeks after 3rd celiotomy. Had extensive recurrences
4. C. G. (239588)	Resection of transverse and descending colon and segments of ileum and jejunum for obstructing metastases from gastric carcinoma resected two years previously.	Lived 2 years, 2 mos. Normally active for almost 2 years following operation
5. O. A. (132357)	Subtotal gastrectomy for carcinoma of stomach with extensive lymph node and omental metastases. Carcinoma had perforated 2 months previously and was repaired in another institution.	Lived 2 years. Normally active during most of this period. Died of metastases

extensive pelvic induration. It was the impression that the obstruction was due to recurrent pelvic neoplasm. Conservative management would have indicated loop-colostomy only. However, since biopsies of the adnexal regions at the time loop-colostomy was done for immediate relief of the obstruction failed to reveal carcinoma, subsequent procedures were carried out to excise the obstructed segments of pelvic colon and in each instance it was discovered that the lesion was irradiation necrosis, ulceration and stenosis of the colon. At present both these patients are living and well four years after final reëstablishment of continuity of the bowel.

FIG. 2 (Continued)



C

FIG. 2C.—Case 332950: Photograph of surgical specimen showing: (T) large carcinoma of transverse colon; (O) entire omentum; (S) spleen; (St) lower half of stomach; (H) transected colon at hepatic flexure; (D) transected colon at junction of descending portion with sigmoid. Body and tail of pancreas and left adrenal gland also resected are on reverse side of specimen and hence not seen. Duration of operation: 3 hours and 20 minutes. He received 1,100 cc. of blood and 2,300 cc. of normal saline solution.

The patient is well and at work full-time in usual occupation, 18 months after operation. He requested and received repair of ventral hernia (incisional) 12 months after above operation and at this time exploration of the abdomen revealed no evidence of recurrences or metastases.

A recapitulation of the results discussed above is given in Table III.

DISCUSSION.—The contraindications for radical extension of operative attack upon advanced abdominal cancer are: (a) widespread peritoneal metastases; (b) extensive hepatic metastases; and (c) inability to encompass the growths by the incisions for resection. However, there may be exceptions to these "rules." For example, in one instance of carcinoma of the body of the pancreas producing very severe pain and found to have numerous intrahepatic

TABLE III

RECAPITULATION OF RESULTS

Total number of patients	100
Operative mortality	34%
Survived operation up to 5.5 months—little or no palliation	14%
Survived operation up to 14 months—received palliation	23%
Living up to 12 months after operation—receiving palliation	12%
Survived operation average of 2.5 years—returned to usual activities but since died of carcinoma	5%
Surviving operation, average of 4 years, returned to normal full-time activities	12%*

* Two patients (2%) following radical resections proved not to have recurrent carcinoma, although latter was initially present, as confirmed by biopsy, as previously described.

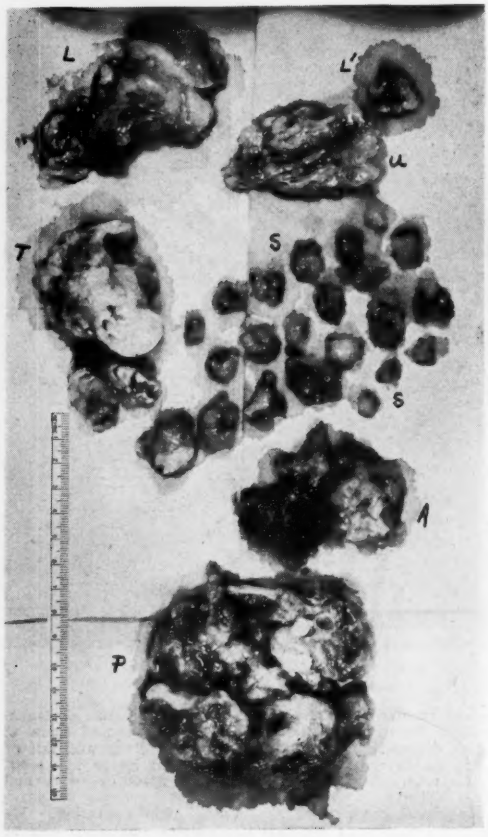


FIG. 3.—Case 274690: Photograph of multiple metastases excised from various portions of the abdomen 4 years after previous operation at which time primary cystadenocarcinoma of right ovary was resected with drainage of pseudomucinous peritonitis. (L L') metastases removed from anterior surfaces of right and left lobes of liver, respectively; (S) metastases removed from serosal surfaces of jejunum and ileum; (U) metastases removed from mesentery of jejunum; (T) metastasis removed from mesentery of ileum; (A) metastasis resected from right lower quadrant of abdominal wall with portion of rectus muscle; (P) mass of recurrent carcinoma excised from cul-de-sac of Douglas. The patient continues in full-time occupation, has maintained 30-pound weight gain and is otherwise well 9 months after operation.

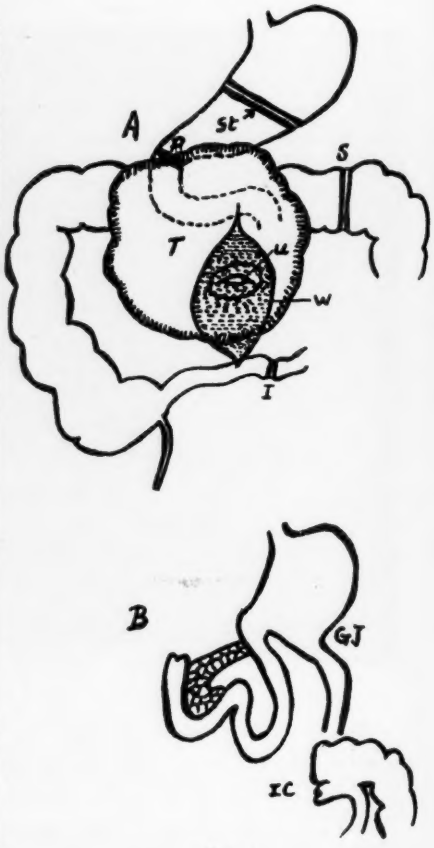


FIG. 4

FIG. 4A.—Case 287119: Diagram showing levels of transection; (St) through midportion of stomach; (P) pylorus; (S) splenic flexure of stomach; (I) lower ileum; (U) umbilicus and (W) surrounding portion of abdominal wall invaded by (T) large carcinoma primary in central portion of transverse colon. The umbilicus and abdominal wall were resected *en masse* with the neoplasm, *etc.*

(B) Situation at the termination of the operation; (GJ) gastrojejunostomy; (IC) ileotransverse colostomy (splenic flexure).

metastases, (the patient was a physician), resection of the body of the pancreas and spleen was, nevertheless, carried out. During the five and one-half-weeks period of survival pain was almost completely relieved. This may well have been due to interruption of sympathetic nerves. In a young male combined abdomino-perineal resection was performed for carcinoma of the colon in the face of diffuse hepatic (but no peritoneal) metastases, since rectal tenesmus was very severe. Relief from this was obtained and the patient survived seven

FIG. 4 (Continued)

C

FIG. 4C.—Case 287119: Photograph of surgical specimen consisting of (TT') large carcinoma arising in and involving right transverse and hepatic flexures of colon that extended upward onto stomach, the lower half of which was resected, and anteriorly along falciform into anterior abdominal wall. (U) Umbilicus and surrounding shaded area indicates extent of abdominal wall (skin, fascia and musculature) also removed to encompass tumor. (I) transected ileum about 8 cm. above cecum; (a) ascending colon; (sp) splenic flexure; (O) omentum. Operation terminated by ileosplenic flexure colostomy. Duration of operation: 3 hours and 15 minutes. Received 1,200 cc. blood and 1,500 cc. normal saline solution. Patient living and well 3 years 6 months after operation, with no evidence of recurrences.

months, gaining ten pounds in weight and was ambulatory for most of this period. A young adult female (Case 274690) patient, weighing 90 pounds, was subjected to exploratory celiotomy because of marked swelling of the abdomen. Extensive peritoneal implants from cystadenocarcinoma of the right ovary were found. The ascites was drained and ovaries removed together with much of the diffuse metastases. Roentgenotherapy was subsequently administered and for four years she returned to normal activity. On the occasion of a follow-up visit a mass was palpable in the cul-de-sac of Douglas and deep induration was present in the right lower quadrant of the abdominal wall. There were no complaints, the 30-pound weight gain was maintained. Nevertheless, celiotomy

was performed and numerous metastases excised from the surfaces of the small bowel, anterior surfaces of the right and left lobes of the liver, from within the mesentery of jejunum and ileum, a mass was resected from the cul-de-sac of Douglas, and muscularis invaded by tumor was resected from the abdominal wall in the right lower quadrant (Fig. 3). Recovery was prompt and in a few weeks she returned to her usual occupation as an office worker. She remains well nine months after the above operation.

It would be difficult to attempt prognosis in individual patients as to whom might receive effective palliation and who would not receive benefits from radical excision. The decision to proceed with operation is governed by several individual factors but obviously when all macroscopic evidence of neoplasm can be resected, there are definite opportunities for effective palliation. On the basis of the experiences summarized above, 50 per cent of patients representing a group hitherto regarded as beyond hope of appreciable benefits from radical surgical therapy were afforded some measure of relief which it is believed could hardly have been received by conservative procedures. The surgical mortality, *i.e.*, 34 per cent, was not excessive given the situations encountered and especially when exploratory celiotomy alone in advanced gastric cancer is reportedly 20 to 25 per cent and for total gastrectomy in general hands is probably in excess of 70 per cent. Increased experience will permit of better judgment in the performances of radical resections for advanced abdominal cancer as well as refinements in technic.

CONCLUSIONS

Progress in supportive treatment of the surgical patient permits of the extension of radical surgical attack upon advanced abdominal cancer. Experiences in a series of 100 patients revealed that effective, albeit in some instances brief, palliation was afforded in 35 per cent with appreciable and prolonged palliation achieved in an additional 15 per cent of the series. Given adequate conditions, a more radical attitude in regard to the surgical treatment of advanced abdominal cancer would appear justifiable.

REFERENCE

[1] Brunschwig, A., Ricketts, H. T., and Bigelow, R. R.: Surg., Gynec. and Obst., 80, 252-256, 1945.

SURGICAL RELIEF OF TREMOR AT REST

PAUL C. BUCY, M.D.

CHICAGO, ILL.

FROM THE ILLINOIS NEUROPSYCHIATRIC INSTITUTE AND DEPARTMENT OF NEUROLOGY AND NEUROLOGICAL SURGERY, UNIVERSITY OF ILLINOIS, CHICAGO, ILL.

THAT TREMOR AT REST arises from the activity of the precentral cortex (regardless of the location of the lesions responsible for the disease) has gradually become increasingly clear. In 1817, Parkinson[11] noted in his Case 6 that the tremor at rest, which had been generalized, was abolished from the right side during the two weeks that side was paralyzed as the result of an apoplectic seizure. Patrick and Levy,[12] in 1922, and Balser,[1] in 1942, made similar observations. However, in such cases the damage from the cerebrovascular disease has been too extensive to permit one to determine accurately the cortical area and the pathway primarily concerned with the production of tremor (Balser[1]). In addition, in 1937, I had abolished both tremor at rest and intention tremor from the right upper extremity by extirpating the "arm" area from areas 4 and 6 of the left precentral gyrus and the neighboring frontal convolutions.[7] This observation definitely established the fact that these tremors, though probably released by destructive lesions in the subcortical nuclei, are produced by nervous impulses arising from the precentral motor cortex (areas 4 and 6). However, it left doubt as to whether these impulses responsible for the involuntary movements of tremor are mediated *via* the pyramidal fibers from area 4 or the extrapyramidal fibers from areas 4 and 6. Putnam[13] helped to clarify this question. In 1938, he demonstrated that tremor at rest is abolished by section of the lateral pyramidal tract in the cervical spinal cord. He subsequently confirmed this observation in several additional cases.

Fibers in the pyramidal tract arise from various places other than the precentral motor cortex (Tower[14]). Whether these nonprecentral origins are confined to the cerebral cortex (particularly the parietal region), as Mettler[10] believes, is not as yet a matter of general agreement. However, the clinical observations cited above demonstrate that only those pyramidal fibers arising from the precentral region are concerned with the production of tremor and in the precentral region pyramidal fibers arise only from area 4 (Tower[14]), which in man is confined to the precentral gyrus (von Bonin[2]). Architecturally, area 4 in man is divisible into three parts: area 4γ, area 4a and area 4s (von Bonin[2]), all of which probably contribute to the pyramidal tract. However, the large pyramidal fibers (over 9μ), which form only two to three per cent of all of the pyramidal fibers, probably arise from the Betz cells which are to be found only in area 4γ. Area 4γ, in turn, forms the posterior part of the precentral gyrus (Fig. 1). The possibility existed that only the Betz cells and these large fibers are concerned with the production of tremor. If this

were true then cortical extirpations could be restricted to the posterior part of the precentral gyrus (area 4γ), and areas 4a, 4s and 6 could be preserved. It seemed likely that such a limited extirpation would produce less paralysis and leave a more useful extremity than was obtained following the larger extirpation of areas 4 and 6. The following case presented an excellent opportunity to test this possibility.

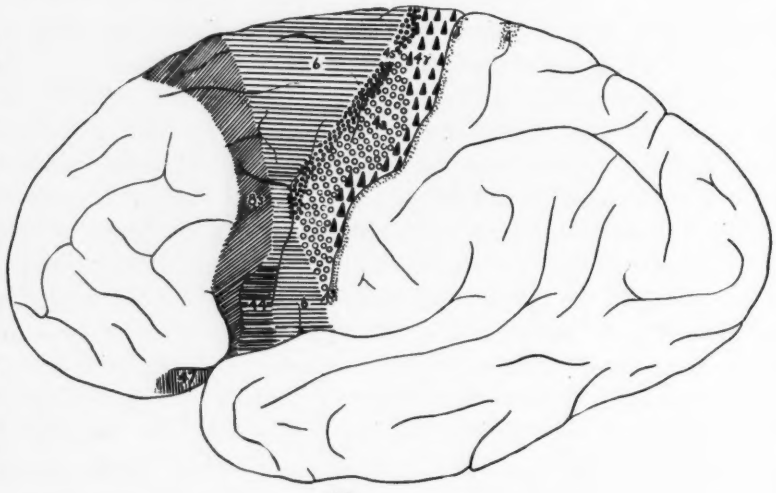


FIG. 1.—The human precentral motor cortex (areas 4γ, 4a, 4s, 6 and 44) and some adjacent areas.

Case Report.—P. di F. was referred by Dr. Daniel H. Levinthal of Chicago, Illinois. He was born in Chicago of Italian parents. He was 23 years of age and single. He had been under observation both in the hospital and in the dispensary at the Illinois Neuropsychiatric Institute for some time. On July 29, 1943, he was admitted to the hospital for operation. This young man came complaining of marked weakness of the right arm and leg and of a tremor, involving these extremities, for 15 years, since he was eight years old. His father informed us that the patient had been a normal healthy child until about the age of 5.5 years, when he had a rather severe attack of "influenza," or "pneumonia." He was ill for approximately three or four weeks. The exact nature of this illness we were unable to learn. However, he seemed to recover from it completely and to remain well until two years later, when he was 7.5 years old. At that time his school teacher noticed that he was beginning to limp and that the right extremities were weak. A short time later a tremor appeared in these extremities. This was, and always has been, worse on excitement and has disappeared during sleep. It has always been most marked with the extremities at rest, and often disappeared during the execution of voluntary movements. The termor and weakness gradually increased in severity, and, whereas, originally the tremor was not constantly present, it was present during all of his waking hours for the five years prior to admission. For three years, that is, since the age of 20, his speech had been much more indistinct than formerly.

Nothing else in the patient's past medical history or in the family history seemed relevant to his present condition.

Physical Examination.—The temperature, pulse and respiratory rate were normal, the blood pressure was 120/76. He was a fairly well-developed and well-nourished white man, with an expressionless face and a marked tremor of the extremities on the right side of his body. He spoke haltingly, and it was at times with difficulty that he was

understood. He was said to be right-handed. He walked with a marked limp, favoring the right lower extremity. There was a scoliosis and a rotation of the trunk, such that the right hip was thrown posteriorly and the right shoulder thrown anteriorly, and he leaned toward the right side. The general physical examination was otherwise negative. The cranial nerves were intact except that the left pupil was slightly smaller than the right and slightly irregular. Both reacted normally to light and on accommodation. There were no oculogyric crises. There was a slight transient nystagmus, particularly on looking to the right. At times fasciculation of the masseter muscles on the left side was seen. There was a definite right lower facial weakness, both on volitional and emotional movement. Auditory acuity was reduced slightly bilaterally. The right shoulder was held elevated and thrust forward. There was, however, no weakness of the sternocleidomastoid muscle or of the trapezius. The tongue protruded in the midline. Because of the violent tremor involving the right extremities, it was difficult to appraise the tendon reflexes. It was finally concluded, however, that they were definitely increased throughout the entire right side of the body, although they were normally active on the left side. The abdominal reflexes were active bilaterally, as were the cremasterics. Hoffmann's sign was not present. The jaw jerk seemed to be increased. There was a suggestive Babinski sign on the right side only. No clonus was elicited. There was weakness at the wrist on the right side but the grasp was quite strong. There was also weakness of the movements of the thumb and the fingers on the right side. Otherwise strength in the right upper extremity was good, although useful activity was practically prevented by the rigidity and the tremor. There was some weakness of the right lower extremity. He walked with a typical spastic hemiplegic gait, tending to drag the foot and circumduct it. The lower extremity was also internally rotated, so as to throw the greater trochanter forward. Actual weakness of the lower extremity, when individual groups of muscles were tested, was, however, slight. There was definite reduction in the volume of the muscles throughout the entire right side. This was perhaps most noticeable in the interossei of the hand. There was definite cogwheel rigidity throughout the right side. There was a pes equinus deformity of the right foot, with contracture of the gastrocnemius and soleus muscles on that side. There was definite diminution in size of the gluteus muscles on the right side. Finger-to-nose and heel-to-knee tests were reasonably well done except that on the right side the tremor interfered somewhat with these tests. Sensation in all forms was intact everywhere.

There was a marked tremor involving both the right upper and lower extremities. The oscillations were at approximately three to four per second. They involved the entire extremity but were most pronounced in the distal half. There was a tendency toward pill-rolling in the right hand, and a marked flexion tremor at the wrist. Both the tremor and the rigidity were more marked in the right upper than in the lower extremity. The tremor was predominantly a tremor at rest, although it was not completely absent during voluntary movement. He had a rather expressionless face; his speech was slow and drawling and hesitant. At times it seemed as though there were a slight motor aphasia in that he did not finally say the word that he started with. However, on detailed tests for aphasia, there were no definitely positive findings. He was slow in his responses, his intelligence was not above average, and he occasionally stuttered. A diagnosis of unilateral right parkinsonism resulting from a chronic encephalitis was made and was concurred in by all who saw and examined him.

Laboratory Data.—Urinalysis was negative, the blood count was normal, the Wassermann and Kahn tests on the blood were negative. A lumbar puncture was made, the cerebrospinal fluid contained 9 mg. of protein per 100 cc. of fluid, the Wassermann test was negative, the colloidal gold curve was flat, and the fluid contained two cells per cubic millimeter. An electro-encephalogram was made, which showed some spike-like waves of slow frequency to either side of the midline in the frontal region.

The patient was given hyoscine hydrobromide and tincture of stramonium without benefit.

Operation.—On August 3, 1943, under ether anesthesia, an osteoplastic flap was reflected in the left parietal region, exposing the central sector of the cortex of the left cerebral hemisphere up to the midline, and with the fissure of Rolando in the middle of the operative field. The exposed cortex did not appear abnormal. Photographs were taken of it (Fig. 2) and a sketch of the cortex was made by Dr. Percival Bailey (Fig. 3). All of the exposed cortex was then carefully stimulated with a 60-cycle sine wave current, using a bipolar electrode. Motor responses were obtained only from the posterior part of the precentral gyrus (Fig. 3). As noted in a previous publication

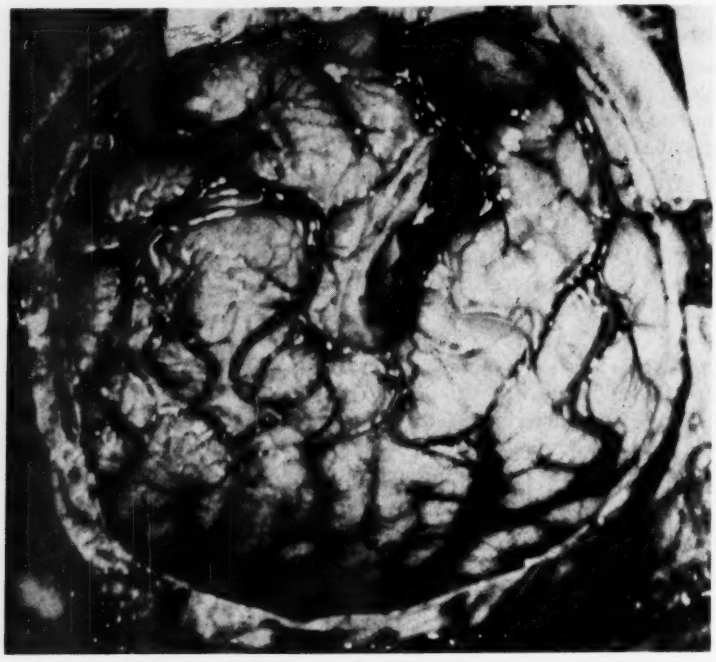


FIG. 2.—Photograph of the left central region after extirpation of the posterior half of the precentral gyrus and, thus, of area 4γ in the "arm" and "leg" fields.

with Dr. Garol,[9] stimulation of an area just anterior to the precentral gyrus and just ventral to the posterior end of the first frontal sulcus or superior frontal sulcus, caused a suppression of peripheral motor response. This area presumably corresponds to area 4s in the subhuman primates. As this response was previously described in detail,[9] it need not be further alluded to here. The threshold for motor responses from the posterior part of the precentral gyrus was 1.6 volts. Movements were elicited in the head region and in both the right upper and lower extremities, as indicated on the accompanying diagram (Fig. 3). When the current was increased to 2.5 volts, a typical motor afterdischarge was produced. The posterior one-half of the precentral gyrus in those regions from which movement of the right upper and lower extremities had been produced, was then removed subpially down to the bottom of the central sulcus (Fig. 2). The great rolandic vein and the communicating vein, which crossed the region of the extirpation were left intact. The extirpation extended down the medial surface of the hemisphere to the first sulcus. The dura mater was then closed tightly, the osteoplastic flap replaced and held in place with silk sutures and the scalp wound closed as usual.

Postoperative Course.—The operation was completed at 4:30 P.M. At 6:00 P.M., the patient was awake and able to coöperate in a limited examination. There was a com-

plete paralysis of the right upper extremity, and although there was marked weakness of the right lower extremity, he was able to flex the hip. There was definitely increased resistance to passive stretching of the flexors of the right upper extremity. All tendon reflexes on the right side were hyperactive; clonus could be elicited at the right ankle; Hoffmann's sign could be elicited in the right hand; Babinski's sign was present on the right side; the right abdominal reflexes were absent; but the cremasteric reflexes were all present; there was a right facial weakness; all sensation was intact, including

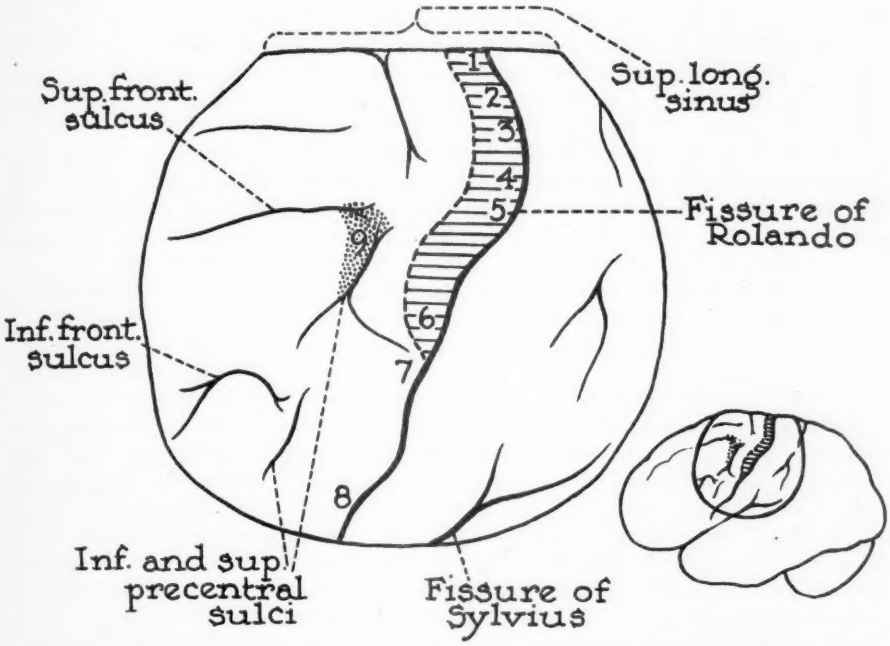


FIG. 3.—Artist's elaboration of a sketch of the cerebral cortex exposed at operation. The insert indicates the general relation of the exposed cerebral cortex. The numbers designate areas of various responses to electrical stimulation. The area for flexion of the right hip is indicated by 1; for contraction of the right quadriceps femoris muscle, by 2; for contraction of the right pectoralis major muscle, by 3; for flexion of the fingers of the right hand, by 4; for flexion of the right elbow and wrist, by 5; for movement of the neck and right shoulder, by 6; for movement of the right corner of the mouth and contraction of the right platysma myoides muscle, by 7; for movement of the lower lip on the right side, by 8, and for the suppressor area—areas 4s, by 9. The area which was extirpated has been indicated by cross-hatching.

light touch, pain sensibility as determined by pinprick, the perception of differences in temperature, vibratory sense, position sense and the recognition of the shape of objects (stereognostic sense).

On the first postoperative day (8-4-43), at 9:00 A.M., his speech was the same as before operation. He was able to abduct the right arm at the shoulder for about 10° to 15°. This movement was performed only after a considerable latent period and with considerable difficulty. He was also able to flex the right elbow after a considerable latent period, and also weakly. He could flex the right hip quite well, probably as well as he could before operation. He was able to extend the right knee about 50 per cent as well as prior to operation. However, he was unable to flex the knee or to move the ankle, the toes, the wrist or the fingers. There was a moderately increased resistance to passive flexion of the elbow, but only after the elbow had been flexed to 90° and a similar resistance to passive extension of the right elbow, after it had been extended to approximately 135°. There was a definite reduction in the sense of position in the right fingers to approximately 50 per cent of absolute accuracy. However, he

was conscious of each passive movement of the finger, and he was able to identify each finger touch accurately. With his eyes closed he erred by as much as six to ten inches in trying to find his right hand with the left. There was no reduction in pain sensibility, as tested with pinprick on either side. All of the tremor which had been present preoperatively was completely abolished and remained so thereafter. There was marked perspiration, involving the entire right arm and right leg, while the left extremities were perfectly dry. Babinski's sign was present.

On the second postoperative day, the right abdominal reflexes had returned, but they were not as active as those on the left side. The cremasteric reflexes, however, were equally active on the two sides. The marked perspiration continued on the right side of the body and involved the head, right arm and upper part of the trunk more than it did the lower part of the trunk and the right lower extremity. Position sense was grossly defective in the right fingers but quite accurate in the toes.

Movement in the right upper extremity was much less than it had been on the first postoperative day and was reduced to limited feeble twitch-like movements at the right shoulder. Movement in the right lower extremities were, likewise, reduced as compared with the first postoperative day. Resistance to passive movement in both the flexors and extensors, in both the upper and lower extremities, on the right side, was more marked. On August 7th, the fourth postoperative day, the excessive perspiration on the right side of the body still continued. The tremor was still completely abolished. He was able to identify individual fingers on the right side, but his sense of position in the right fingers and his ability to find the right hand with his left hand when his eyes were closed was grossly defective. Vibratory sense was only very slightly diminished on the right side. Sense of position was excellent in the toes and at the wrists. The reflexes were the same as they had been on the first and second postoperative days. Perception of pinprick was normal and the perception of alterations in temperature was acute over his entire body. The ability to recognize objects with his right hand, although not abolished, was definitely impaired. He could recognize numbers written on the palms of the hands, but on the right side it was necessary for these numbers to be three and one-half centimeters high, whereas numbers one and one-half centimeters high were properly recognized on the left side. He was able to detect gross differences in the weight of objects placed in his right hand. Movements at the right shoulder and elbow continued to increase in strength, but there was still no movement at the wrist or of the fingers. Likewise, movements of the hip and knee on the right side continued to increase, whereas there was still no movement at the ankle or of the toes. This condition continued gradually to improve. By the twentieth postoperative day, August 23, 1943, the tremor continued to be entirely abolished; he was able to walk almost as well as before the operation and he had become able to flex his fingers, but could not extend them. In the lower extremities individual movements at the hip and knee had continued to gain in strength, but he was unable to move the ankle or the toes. There was a slight increase in resistance to passive movement on the right side. All tendon reflexes on that side were markedly increased and Babinski's sign was still present. Clonus could be elicited at both the knee and ankle. Hoffmann's sign was present on the right side. Both the abdominal and cremasteric reflexes were active on both sides of the body. There was no disturbance of sensation including light touch, pinprick, alterations in temperature, vibration and position sense. On September 4, 1943, one month after the operation, the patient was discharged from the hospital. The tremor was still completely abolished, and has remained so up to the present time.

By September 30, 1943, almost two months after the operation, he was walking better than prior to the operation. He was able to shake hands using his right hand. Strength in the right extremities had improved greatly. He now could not only flex the right hand and fingers, but could extend the fingers and thumb as well. In October he obtained a job in a laundry handling bundles, but he found that he had to discontinue

it because of difficulty in maintaining his balance when attempting to carry bundles and walk up stairs. By January 4, 1944, five months after the operation, he was able to tie his shoes and his necktie, using both the right and the left hand, to grasp. His right hand had increased in strength.

On May 3, 1944, nine months after the operation, he was able to walk with his body upright, although with a definite hemiparetic gait. He did not swing his right arm as he walked. There was a definite moderately spastic hemiparesis on the right side, much the same as prior to the operation. All tendon reflexes were increased on that side. Hoffmann's sign was present on the right side, as was Babinski's sign. Ankle and patellar clonus were still readily elicited. The musculature on the right side was definitely atrophic as compared with the left, just as it had been prior to the operation. There was no disturbance of sensation anywhere. The violent tremor at rest which had been present prior to operation had never returned. His speech was still slow and rather monotonous as it had always been. When last seen, on December 13, 1944, over 16 months after the operation, the tremor was still absent. Useful voluntary movements of the right upper extremity were very limited. He walked better than before the operation, although in a similar fashion.

DISCUSSION.—These observations present several points of interest, particularly as concerns the effect of the extirpation of area 4γ upon tremor at rest, upon paralysis and spasticity, upon sensation and upon perspiration.

Tremor: Extirpation of the "arm" and "leg" portions of area 4γ (the posterior part of the precentral gyrus) abolishes tremor at rest in the contralateral upper and lower extremities. The tremor was abolished immediately after the operation and has not returned during the subsequent 16 months that the patient has been observed. This would indicate that tremor at rest arises from the activity of the Betz cells and is produced by nervous impulses mediated by the large (9 to 22μ fibers), which form two to three per cent of the pyramidal tract.

These conclusions relative to the mechanism responsible for the actual production of tremor at rest have no bearing upon the question of what structures must be destroyed for tremor at rest to appear. It is very likely, as I[5] have previously noted, that destruction of the substantia nigra or of the globus pallidus, or of both, is the most common lesion which releases the pyramidal system to this form of abnormal hyperactivity.

Paralysis: This young man was not the ideal patient upon which to determine the degree of paralysis resulting from the removal of area 4γ. He had some paralysis before the operation. Nevertheless, following the operation he had much more paralysis particularly in the upper extremity and particularly in the distal parts (hand, fingers and foot) than before the operation. In the hand this has prevented much utilization of the upper extremity, although the disability has been somewhat less than in those cases where areas 4 and 6 were removed (Bucy[4]). In the lower extremity the disability does not appear to be much, if any greater than before the operation.

Spasticity: Although the resistance to passive manipulation of the right extremities is not great it is definitely more than before the operation. Furthermore, the tendon reflexes are much more active than before the operation,

clonus is readily elicited and Hoffmann's sign has appeared in a forthright manner. This all strongly indicates that in man inhibition of the postural and myotatic reflexes is not limited in the precentral motor cortex to area 4s but is also represented to some degree in area 4γ. Admittedly, this case does not definitely establish that as a fact for there is no evidence as to possible operative or postoperative damage to area 4s.

Sensation: This case, along with previous similar observations (Bucy[6]), leaves little doubt that the precentral gyrus is not concerned with the conscious perception of sensory stimuli. Earlier, many individuals had observed that removal of the precentral gyrus results in impairment of some forms of sensibility on the opposite half of the body. In the vast majority of instances this sensory impairment is temporary. This case clearly establishes the fact that the sensory loss does not appear immediately after the destruction of the precentral tissue as would be the case if it resulted directly from that cortical extirpation. Rather the sensory deficiency appears gradually several hours after the extirpation as would be expected if it were due to the impairment of the circulation of the neighboring structures, notably the postcentral gyrus, from edema and venous thromboses secondary to the operation.

Perspiration: The observation that the right half of the body perspired very profusely for several days after the extirpation is peculiar, in my experience, to this case. This would seem to indicate that area 4γ is concerned with the control of perspiration, probably through the sympathetic system. In this instance the excessive perspiration could be interpreted as resulting from the removal of cortical inhibition from the sympathetic nervous system, releasing it to temporary hyperactivity. Similarly, several years ago, I[3] reported another case in which a presumed capsular hemiplegia was associated with unilateral vascular spasm, abolition of the pulse, inability to obtain the blood pressure, cyanosis and coldness of the paralyzed extremities. In this instance, too, a release of cortical inhibition over the sympathetic nervous system was postulated.

How the present observation correlates with that previously reported with Pribram,[8] in which a tumor beneath the lower end of the right precentral gyrus was associated with epileptiform convulsions of the left half of the face and associated attacks of localized sweating of the left side of the face and left upper extremity, is not as yet entirely clear. Both observations indicate that the precentral region exercises some control over the mechanism of sweating and that control is a localized one, as evidenced by the unilateral sweating in the present case and the limitation of the sweating to a small part of one side of the body in the case recorded with Pribram[8]

Aphasia: In previous cases where a more extensive extirpation of the left precentral region was made for the relief of involuntary movements a temporary motor aphasia developed.[4] In this case, with a much more limited extirpation, there was at no time any such disturbance of speech.

Suppression: Garol and I[9] have already reported the demonstration for

the first time of the suppressor activity of area 4s in the human brain, in this case.

SUMMARY

The case of a young man, 23 years of age, is reported. He suffered from a severe tremor at rest and a mild spastic hemiparesis involving the right extremities, from the age of eight years. The "arm" and "leg" portions of area 4γ, the posterior part of the precentral gyrus, were removed. This procedure completely abolished the tremor, produced considerable paralysis particularly of the hand and fingers, resulted in some increase in spasticity, caused no immediate disturbance in sensory perception, and was followed by excessive perspiration on the right half of the body for a few days. In this same case, at the time of the operation, the suppressor effect of area 4s was demonstrated for the first time in the human brain.

REFERENCES

1 Balser, B. H.: Alternating Tremor and Its Relation to Cortical Pathways. Arch. Neurol. & Psychiat., **47**, 962-70, 1942.

2 Bonin, G. von: Architecture of the Precentral Motor Cortex and Some Adjacent Areas. Chap. II in *The Precentral Motor Cortex*, edited by P. C. Bucy. University of Illinois Press, Urbana, Ill., 1944.

3 Bucy, P. C.: Vasomotor Changes Associated with Paralysis of Cerebral Origin. Arch. Neurol. & Psychiat., **33**, 30-52, 1935.

4 Bucy, P. C.: Cortical Extirpation in the Treatment of Involuntary Movements. Res. Publ. Assoc. Nerv. & Ment. Dis., **21**, 551-95, 1940.

5 Bucy, P. C.: The Neural Mechanism of Athetosis and Tremor. J. Neuropath. and Exp. Neurol., **1**, 224-39, 1942.

6 Bucy, P. C.: Effects of Extirpation in Man, Chap. XIV, in *The Precentral Motor Cortex*, edited by P. C. Bucy. University of Illinois Press, Urbana, Ill., 1944.

7 Bucy, P. C., and Case, T. J.: Tremor: Physiologic Mechanism and Abolition by Surgical Means. Arch. Neurol. & Psychiat., **41**, 721-46, 1939.

8 Bucy, P. C., and Pribram, K. H.: Localized Sweating as Part of a Localized Convulsive Seizure. Arch. Neurol. & Psychiat., **50**, 456-61, 1943.

9 Garol, H. W., and Bucy, P. C.: Suppression of Motor Response in Man. Arch. Neurol. & Psychiat., **51**, 528–32, 1944.

10 Mettler, F. A.: On the Origin of the Fibers in the Pyramids of the Primate Brain. **57**, 111–13, 1944.

11 Parkinson, J.: An Essay on the Shaking Palsy. London, Sherwood, Neeley and Jones, 1817; reproduced in Ostheimer, A. J.: A bibliographic note on "An Essay on the Shaking Palsy," by James Parkinson, M.D., Member of the Royal College of Surgeons, Arch. Neurol. & Psychiat., **7**, 681–710, 1922.

12 Patrick, H. T., and Levy, D. N.: Parkinson's Disease. Arch. Neurol. & Psychiat., **7**, 711–20, 1922.

13 Putnam, T. J.: Relief from Unilateral Paralysis Agitans by Section of the Pyramidal Tract. Arch. Neurol. & Psychiat., **40**, 1049–50, 1938.

14 Tower, S. S.: The Pyramidal Tract. Chap. III in *The Precentral Motor Cortex*, edited by P. C. Bucy. University of Illinois Press, Urbana, Ill., 1944.

TRANSTHORACIC ESOPHAGOGASTROSTOMY FOR BENIGN STRICTURES OF THE LOWER ESOPHAGUS

DWIGHT EDWIN CLARK, M.S., M.D.,* AND WILLIAM E. ADAMS, M.D.

CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY OF THE UNIVERSITY OF CHICAGO, CHICAGO, ILL.

BENIGN OBSTRUCTION OF THE ESOPHAGUS, particularly at the lower end, may follow trauma, esophagitis, corrosion, simple peptic ulceration and chronic granulomas. Strictures of the esophagus associated with generalized scleroderma has been describe dby Lindsey, Templeton and Rothman.[1] In a certain number of cases no etiologic factor can be determined. In a series of 243 cases of benign strictures Vinson[2] found 40 of unknown origin. Strictures are less frequently observed than carcinomas or cardiospasm, but, as Yudin[3] pointed out, attract attention and interest because many of the cases concern young adults doomed either to repeated dilatations or to a miserable existence with a gastrostomy.

None of the five cases which form the basis of this report was considered to have cardiospasm. In one case the stricture followed the ingestion of lye, another was associated with generalized scleroderma,† and in three of the cases no etiologic factor could be ascertained. In all of the cases the obstruction either started above the diaphragm, or the entire lesion was in the thorax, so that none was amenable to a transabdominal cardioplasty.

It is said that stricture of the esophagus with complete anatomic stenosis seldom occurs and that gradual dilatation will eventually result in restoration of swallowing in most cases. In order to be successful, treatment requires the coöperation of the patient as well as skill and perseverance on the part of the physician.

It is that small group in which conservative treatment fails, that becomes of interest to the surgeon. Four of our cases had repeated dilatations, with only temporary relief, and two of these required gastrostomies when dilatations became impossible. The fifth case was not subjected to dilatation because a malignancy of the cardia was suspected.

In reviewing the literature, very little can be found concerning the surgical treatment of benign strictures of the lower esophagus. Yudin[3] recently has reported construction of an artificial esophagus in 80 cases of stricture of the esophagus. In six of these he used Birher's cutaneous method. Sixteen cases had a direct anastomosis of the pharynx to a jejunal transplant and 58 were operated upon by the combined methods, using a segment of jejunum for the lower part and a skin tube above.

Such procedures as Yudin describes may be applicable for strictures

* On active service with the United States Army.

† This case was previously reported by Lindsey, Templeton and Rothman.[1]

above the arch of the aorta but are certainly not ideal for lesions of the lower esophagus.

Transthoracic esophagogastrostomy was performed successfully on five cases of benign stricture of the lower esophagus. There were no deaths. Since review of the literature failed to reveal the use of such a procedure for lesions in this location, it was thought a report would be of interest even though the number of cases is small.

Most of the patients with a long-standing stricture of the esophagus are undernourished, which increases the possibility of postoperative complications. Adequate preoperative preparation is extremely important. Administration of fluid, whole blood and plasma will aid materially in enabling the patient to successfully undergo an operation. Four of the patients in our series were given sulfonamides preoperatively and one was digitalized (Case 4).

METHOD OF PROCEDURE

Positive pressure ethylene-oxygen-ether ansthesia administered through a snug-fitting face mask was used. The patients were placed on their right side with the left arm suspended from a rectangular frame. The left chest and the abdomen were prepared for operation, and an ankle vein was prepared for intravenous injection. The chest was opened through the eighth rib bed in four cases and through the eighth interspace in one case. Excellent exposure was obtained by the latter approach without resecting any ribs. The lung was retracted mesially and anteriorly, exposing the costovertebral gutter. In the first three cases, the phrenic nerve was crushed, but in the last two cases a long segment of the phrenic nerve was excised in order to assure a permanent paralysis of the diaphragm. The mediastinal pleura was incised and the lower esophagus isolated, including the accompanying vagi, which were spared wherever possible. In our experience, the lesion was very difficult to identify, and only after very careful inspection and palpation was it possible to determine the level and extent of the stricture. A 12-cm. radial incision was made in the diaphragm from the periphery toward the esophageal hiatus. The left phrenic artery was divided and ligated. In two of the cases the spleen was removed to facilitate mobilization of the stomach. Usually the fundus of the stomach could be brought up readily into the thorax to the arch of the aorta after the upper part of the greater curvature of the stomach had been liberated. The site for anastomosis was selected just above or at the upper level of the stricture. Two umbilical tapes were placed around the esophagus and tied twice, the second tie being a slip-knot, as shown in Figure 1. A side-to-side anastomosis was then made between the fundus of the stomach and the esophagus with two rows of interrupted or continuous linen sutures (Fig. 1). Tension on the suture line was relieved by anchoring the stomach to the pleura above the anastomosis. The diaphragm was closed about the stomach and sutured to its wall. A Pezzar catheter was inserted posterolaterally through the ninth interspace for pleural drainage. The wound was closed

tightly. Blood transfusion was given in every case and was started at the beginning of the procedure. From 600 to 1,800 cc. were administered. The operations required from two to four hours.

POSTOPERATIVE COURSE AND CARE

All of the patients made an uneventful recovery and are still alive and enjoying a normal existence. Four of the cases received sulfonamides intravenously and one (Case 5) was given penicillin intramuscularly. Small amounts of liquids were given *per os* on the fifth to the seventh day, following which the diet was gradually increased. By the tenth to the twelfth day each was taking a soft diet without difficulty. None complained of regurgitation, even at night. The pleural drainage catheter was removed on the fifth to the seventh day.

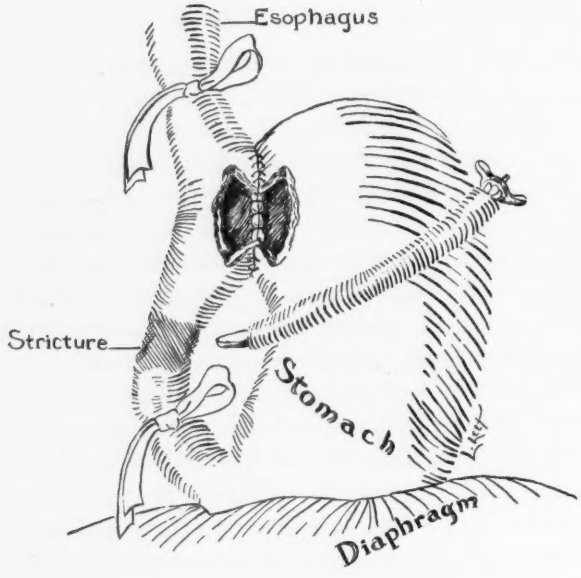


FIG. 1.—Diagram showing side-to-side esophagogastrostomy above the level of the benign stricture.

CASE REPORTS

Case 1.—P. V., a male, age 26, was admitted to the hospital, September 6, 1941, complaining of difficulty in swallowing which had begun approximately three years previously. Liquids as well as solid foods seemed to stick beneath the sternum, and he obtained relief only after most of the ingested food had been regurgitated. He had lost 45 pounds of weight during the three-year period. Two years before admission a diagnosis of a stricture of the lower esophagus was made, and repeated dilatations were performed, which would give him relief for one to two days. Antispasmodics afforded him very little benefit. No etiologic factor could be ascertained. Past history, family history and social history were not significant.

Physical examination revealed a well-developed young man with obvious signs of

considerable weight loss. The blood pressure was 112/70. Detailed examination revealed no abnormal findings.

Laboratory examinations showed white blood count 8,600; hemoglobin 12.8 Gm.; and red blood count 4,400,000. Wassermann and Kahn tests were negative. Urine was negative. Roentgenologic studies of the esophagus following the ingestion of barium revealed a stricture of the lower esophagus which began about two centimeters above the diaphragm (Fig. 2).

The patient was very despondent and refused dilatations or any form of conservative therapy. On September 9, 1941, a transthoracic esophagogastrostomy was performed. His recovery was uneventful, and he was discharged on the 13th postoperative day. Roentgenograms of the esophagus and stomach after the ingestion of barium made on the day of his discharge revealed a well-functioning esophagogastrostomy (Fig. 3).

Within a few months he had regained all of his lost weight and was able to eat any food without experiencing any difficulty.

Case 2.—S. S., age 40, was admitted to the clinics August 1, 1942. He complained of progressive difficulty in swallowing for seven years. Dilatation was first undertaken two years after the onset of dysphagia and was repeated at irregular intervals, with only temporary relief until December, 1941. At this time the obstruction became almost complete and dilatation was unsuccessful. A gastrostomy was performed, through which he received all of his nourishment. Retrograde dilatations were attempted with the aid of a string in the esophagus but these were, likewise, unsuccessful. He had lost 47 pounds of weight and had become quite weak.

About 1.5 years after the onset of the dysphagia, the skin on his hands, feet and face began to tighten and become atrophic. The condition became progressively worse, and he developed repeated ulcers on his fingers which healed very slowly. Past history was irrelevant.

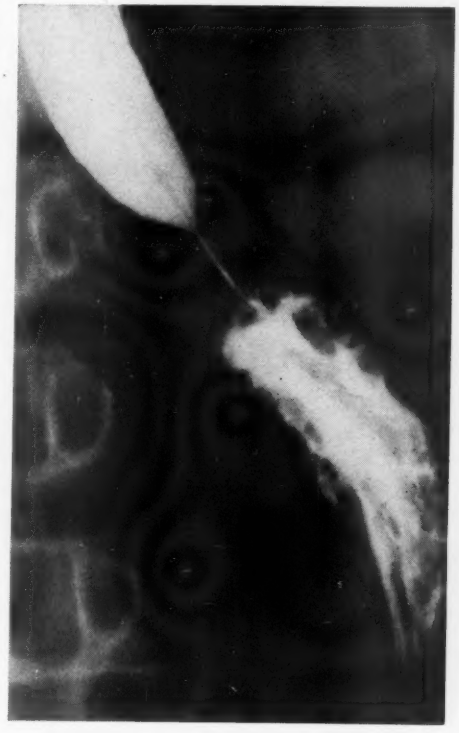


FIG. 2.—Case 1: Roentgenogram of the esophagus and stomach following the ingestion of barium showing a marked narrowing of the lower esophagus. The stricture begins about 2 cm. above the diaphragm.

Physical examination showed a fully developed, easily recognizable, generalized scleroderma, with the characteristically stiff and atrophic appearance of the face and the hands (Fig. 6). There was a large gastrostomy opening in the upper abdomen into which a large rubber tube was inserted. Considerable gastric juice leaked from around the tube and the skin on the upper abdomen was markedly excoriated.

Laboratory Data: White blood count 6,850; hemoglobin 13.5 Gm.; red blood count 3,870,000. Urine was negative, Wassermann and Kahn tests were negative. Blood chemical determinations were all within normal limits. B.M.R. was plus 1. Roentgenologic examination of the esophagus revealed a smooth narrowing 2 to 3 cm. in length just above the phrenic ampulla (Fig. 4). The barium passed slowly through the stricture. A primary peristaltic wave began in the pharynx and progressed only a short distance

down the esophagus to the level of the sternal notch where it disappeared. A shallow contraction wave continued on down. This wave was not powerful enough nor deep enough to force a bolus ahead of it. No tertiary waves were seen.

At esophagoscopy, the wall of the esophagus from the middle third downward was diffusely reddened and apparently thickened. In the lower third, a diffuse layer of white exudate was present which could be easily separated off, leaving a granulating base. At a distance of 40 cm. from the upper teeth a smooth scar tissue constriction

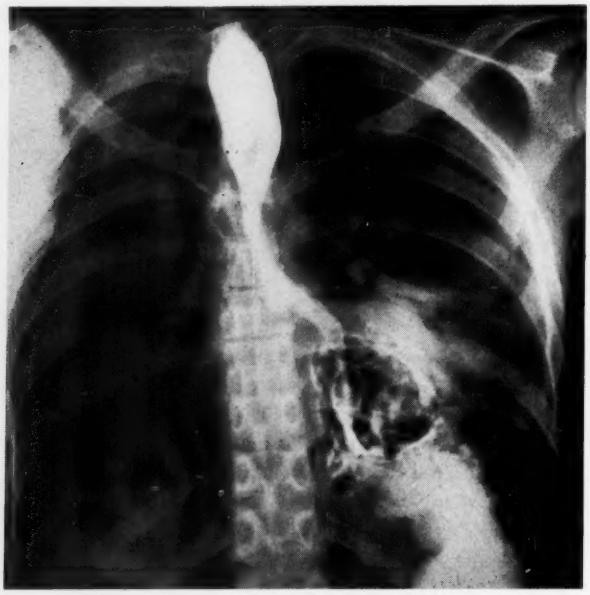


FIG. 3.—Case 1: Roentgenogram of the esophagus and the stomach, 13 days after transthoracic esophagogastrostomy. The site of anastomosis is well shown. The proximal one-fourth of the stomach is in the thorax. Fluoroscopy revealed no obstruction.

was present which did not admit the esophagoscope. There was superficial ulceration in and above the area of the stricture which became apparent when the layer of exudate was removed. A string was present in the esophagus.

In view of the excellent results obtained in the first case it was decided to perform a similar procedure on this patient in spite of the severe changes due to the generalized scleroderma. On September 26, 1942, a transthoracic esophagogastrostomy was performed. A constriction was found approximately 2.5 cm. above the diaphragm. The wall of the esophagus above the narrowing was considerably thickened. He made an uneventful recovery. The gastrostomy was closed one month after the esophagogastrostomy.

Roentgenograms of the esophagus and stomach following the ingestion of barium two weeks postoperatively showed a well-functioning esophagogastrostomy, with no obstruction to the flow of barium (Fig. 5). The physiology of the esophagus was not changed.

COMMENT: Many patients with scleroderma develop benign strictures of the esophagus. Dilatation is difficult because these patients cannot open their

mouths more than one-half the normal width, protrusion of the tongue is limited, and the head cannot be placed satisfactorily because of tightness of the skin over the jaws and neck.

Even though most of the patients with scleroderma and dysphagia show a marked disturbance in the physiology of the esophagus, transthoracic esophagogastrostomy certainly offers them a more comfortable life than a gastrostomy. The pathologic changes in the esophagus did not seem to impair healing.

FIG. 4.—Case 2: Benign stricture of the esophagus just above the phrenic ampulla associated with generalized scleroderma.

Case 3.—Mrs. L. L., age 35, was admitted to the University Clinics October 4, 1943. About 19 years previously she had ingested lye. Two months later she began to have dysphagia which gradually became worse until she had difficulty in swallowing even liquids. A diagnosis of a stricture of the lower end of the esophagus was made, and for eight months she was given weekly dilatations. For the next three years she got along well, after which time she again began to have marked difficulty in swallowing solid foods. During the succeeding eight years she required regular periods of dilatation. As time went on she obtained less improvement from each dilatation. Seven years ago a gastrostomy was performed through which she received most of her nourishment. Since the onset of her dysphagia, she has always been undernourished and weak. Past history was not significant.

Physical examination revealed a very thin woman, who appeared chronically ill. A gastrostomy opening was present in the upper abdomen through which a large rubber tube protruded. The skin over the upper abdomen was excoriated.

Laboratory studies were normal.

Roentgenologic examination of the esophagus after the ingestion of barium demonstrated a high-grade stricture of the esophagus beginning about 11 cm. above the diaphragm and extending downward for a distance of approximately 7 cm. The esophagus above the stricture was somewhat dilated (Fig 7).

On October 10, 1943, a transthoracic esophagogastrostomy was performed. The lower 8 cm. of the esophagus was firmer and thicker than normal, although the exact extent of the lesion was not distinct.

The patient's postoperative convalescence was uneventful. A roentgenologic study of the esophagus with barium at the time of her discharge showed a well-functioning anastomosis between the fundus of the stomach and the lower esophagus (Fig. 8).

The gastrostomy was closed six weeks after the esophagogastrostomy.

Three months after the operation the patient was eating normally and had gained 50 pounds. There was no apparent regurgitation of gastric contents into the esophagus.

Case 4.—Mrs. M. B., age 60, was admitted to Albert Merritt Billings Hospital, May 6, 1944, complaining of difficulty in swallowing for a period of five months. The dysphagia was intermittent and began after an attack of influenza. Solid food caused

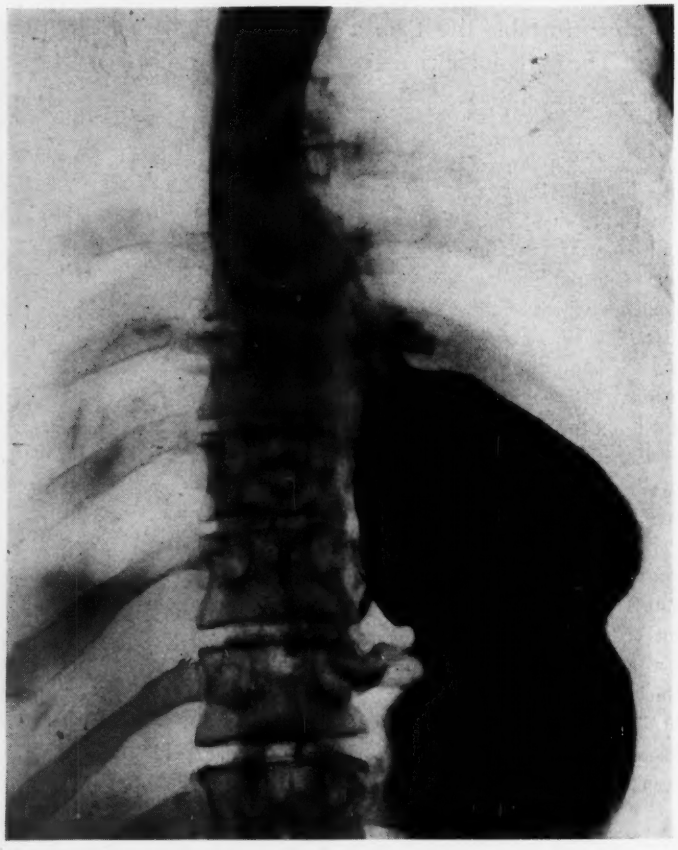


FIG. 5.—Case 2: Roentgenogram of esophagus and stomach following the ingestion of barium, two weeks after transthoracic esophagogastrostomy. A wide anastomosis is shown. The proximal one-third of the stomach is above the diaphragm.

her more discomfort than liquids. Food seemed to stick just beneath the lower sternum. She had some regurgitation, but at other times she would have the sensation of something releasing and her discomfort would disappear. Nervousness or emotional excitement made her condition worse. She had lost 23 pounds in weight and had become quite weak. Past history was irrelevant.

Physical examination was negative except for the obvious evidence of recent weight loss.

Laboratory data disclosed a white blood count of 7,900, with a normal differential; hemoglobin 13.5 Gm.; red blood count, 4,270,000. The urine was negative. Plasma proteins were 6.38 Gm. per cent. Gastric analysis after the administration of histamine revealed free acid in all specimens.

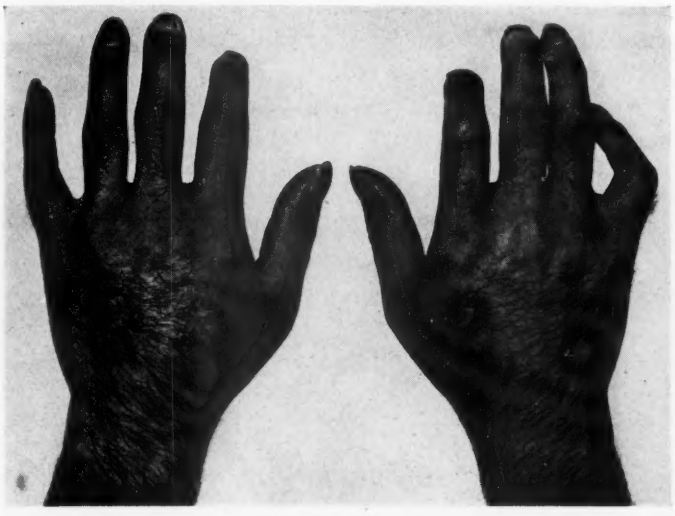


FIG. 6A

FIG. 6.—Case 2: Photograph of hands and face showing the typical changes of advanced generalized scleroderma.

Roentgenologic study of the esophagus and stomach after the ingestion of barium showed a marked narrowing of the lower esophagus which began just above the diaphragm. Under the influence of amyl nitrite the narrowed area dilated to 1 cm. A filling defect was observed in the cardia of the stomach, and was interpreted as a possible malignancy of the stomach (Fig. 9).

On May 19, 1944, the proximal portion of the stomach and the lower esophagus was explored through a transthoracic approach. The filling defect observed at fluoroscopy was found to be caused by redundant mucosa. An esophagogastrostomy was performed, connecting the fundus of the stomach to the lower esophagus.

The patient made an uneventful postoperative recovery, and was completely relieved of her dysphagia. Roentgenograms, taken June 5, 1944, revealed a well-functioning esophagogastrostomy.

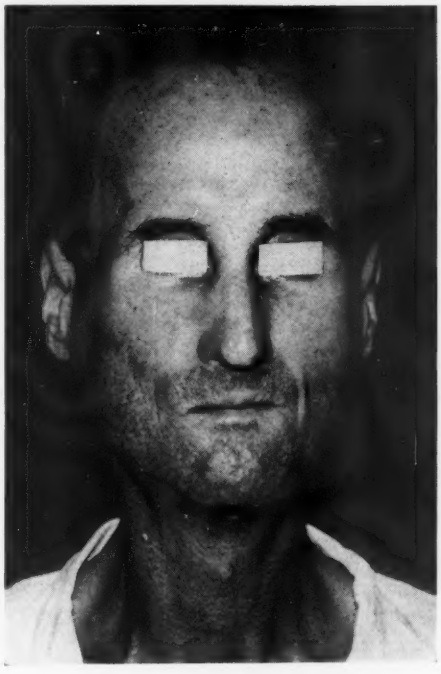


FIG. 6B

COMMENT: Dilatation was not attempted on this patient because of the possibility of malignancy being present. The transthoracic approach was used because it afforded better exposure to the portion of the stomach suspected of having malignant involvement, and it offered a better means of dealing with direct extension into the lower esophagus.

This patient received digitalis preoperatively. Patients in the upper age-group tolerate such surgery much better if they have been digitalized. No adverse reactions have been observed.

Case 5.—J. B., male, age 38, was first seen at the University of Chicago Clinics June 16, 1944. Eight weeks before this date he suddenly began to have difficulty in swallowing solid foods. This difficulty gradually progressed and for two weeks prior

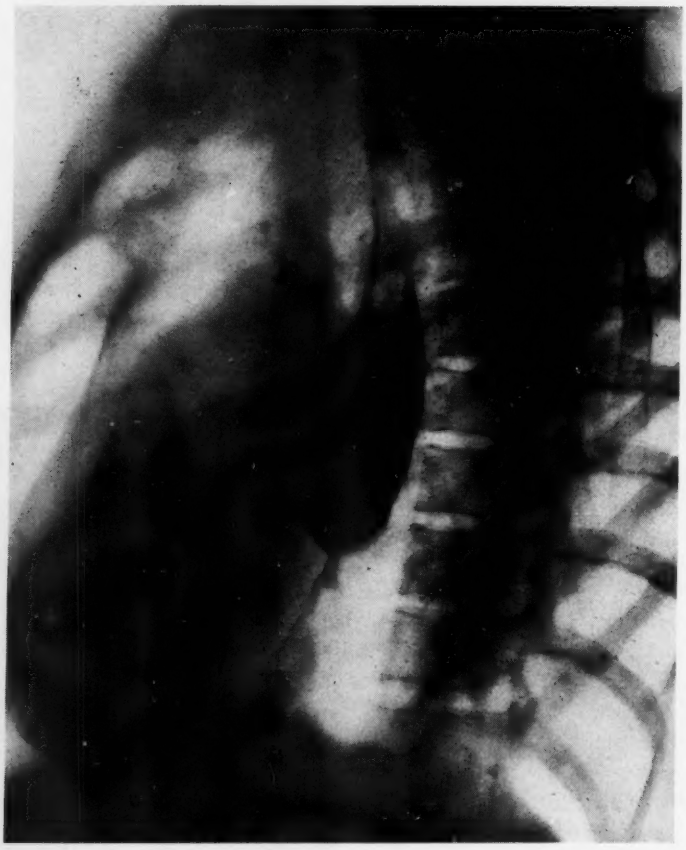


FIG. 7.—Case 3: Shows a long cicatricial stricture of the lower esophagus following corrosion from swallowing lye. The obstruction is almost complete.

to admission he was unable to swallow even liquids. The ingested food seemed to stick beneath the lower sternum, and then it would be regurgitated. He had lost 28 pounds of weight. Past history revealed that he had swallowed a fish bone ten years ago which caused some dysphagia for about two weeks.

Physical examination showed nothing remarkable except for the obvious signs of recent weight loss and dehydration.

Laboratory data showed a white blood count 6,050; hemoglobin 12.5 Gm.; red blood count 3,790,000. Urine negative. Wassermann and Kahn negative. Roentgenologic examination of the esophagus after the ingestion of barium showed an obstruction at the junction of the middle and lower thirds of the esophagus. The obstructing lesion was about 0.5 cm. in length (Fig. 10).

FIG. 8.—Case 3: Roentgenogram of the esophagus and stomach after the ingestion of barium, two and one-half weeks after transthoracic esophagogastrostomy. There is a well-functioning anastomosis and no obstruction to the flow of barium.

FIG. 9.—Case 4: Roentgenogram of lower esophagus and upper stomach after ingestion of barium showing a marked narrowing of the lower esophagus which begins just above the diaphragm. Obstruction is not complete. Irregularity along the fundus was interpreted as possibly due to a carcinoma of the stomach.

FIG. 10.—Case 5: Roentgenogram of lower esophagus after the ingestion of barium showing narrow stricture 8 cm. above diaphragm. Obstruction is almost complete.

The patient was esophagoscoped three times within eight days. A stenosis was observed approximately 8 cm. above the diaphragm. The esophagoscope could easily be passed through the stenosed area, but when it was withdrawn the cicatricial region would snap closed. A No. 20 dilator was passed at the time of each esophagoscopy. Two biopsies removed from the region of the stricture showed chronic inflammation. The patient's dysphagia was not relieved by the dilatations, and he had to be given parenteral fluids daily.

On June 16, 1944, a transthoracic esophagogastrostomy was performed. There was considerable reaction in the mediastinum about the area of stenosis. The lower limit

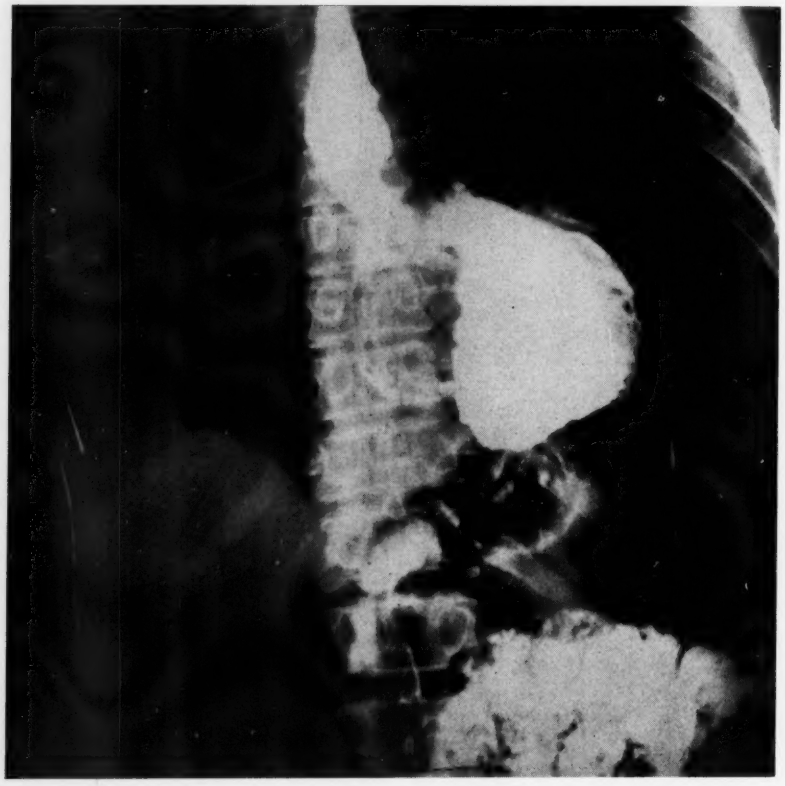


FIG. 11.—Case 5: X-ray eleven days after transthoracic esophagogastrostomy. A wide, well-functioning anastomosis is seen. The esophagus below the stricture is visualized. The proximal one-half of the stomach is in the thorax.

of the anastomosis was made in the stricture. Biopsy obtained from the involved area at the time of operation showed chronic inflammation.

The patient made an uneventful recovery. Roentgenographic study of the esophagus and stomach, which was made on the day of his discharge, showed a well-functioning esophagogastrostomy. Since the stricture was relieved by the operation, the barium flowed readily through the lower esophagus (Fig. 11).

COMMENT: In some cases, even after repeated esophagoscopies and roentgenologic studies, it is difficult to distinguish a benign lesion from a stricture caused by a neoplasm. In such cases the stenosed area should be opened and a biopsy obtained.

SUMMARY

1. Five cases of transthoracic esophagogastrostomy for benign stricture of the lower esophagus are reported. There were no deaths.

2. In selected cases of benign stricture of the lower esophagus, transthoracic esophagogastrostomy offers the patient complete relief of symptoms without the necessity for repeated dilatations or the unpleasantness of a gastrostomy.

3. The technic of the operation is discussed.

REFERENCES

1 Lindsey, J. R., Templeton, F. E., and Rothman, S.: Lesions of the Esophagus in Generalized Progressive Scleroderma. Jour. Amer. Med. Assoc., **123,** 745, 1943.

2 Vinson, P. P.: Cicatricial (Benign) Strictures of the Esophagus of Unknown Origin. Surg., Gynec. & Obst., **52,** 955, 1931.

3 Yudin, S. S.: The Surgical Construction of 80 Cases of Artificial Esophagus. Surg., Gynec. & Obst., **78,** 561, 1944.

THE USE OF PENICILLIN IN THE TREATMENT OF ACUTE HEMATOGENOUS OSTEOMYELITIS IN CHILDREN

REPORT OF TWELVE CONSECUTIVE CASES

EDWARD L. COMPERE, M.D.,
WILLIAM J. SCHNUTE, M.D., AND LEE M. CATTELL, M.D.
CHICAGO, ILL.

FROM THE PEDIATRIC AND ORTHOPAEDIC SERVICES, CHILDREN'S MEMORIAL HOSPITAL, CHICAGO, ILLINOIS, AND THE DEPARTMENT OF BONE AND JOINT SURGERY, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL.

ACUTE HEMATOGENOUS OSTEOMYELITIS is caused, in most cases, by *hemolytic Staphylococcus aureus* or *albus,* or *hemolytic Streptococcus* organisms. Most of the patients are children and, hence, the bones that are involved are growing.

Cases of acute hematogenous osteomyelitis should be divided into age-groups for purposes of discussion or statistical analyses: (1) Under three years of age. (2) Ages three to 14 years. (3) Fourteen to 20 years. (4) Adults.

In very young children the infecting organism is more often the streptococcus. The initial infection may be in the nose, throat, middle ear, vaccination wound, or in the umbilicus of a newborn infant. This organism does not produce as extensive destruction of bone as does the staphylococcus. Furthermore, the bones of infants repair quickly and persistent drainage or extensive sequestration is less common than in older patients.

Hematogenous osteomyelitis in children, age three years to puberty, is secondary in most cases to some small area of infection in the skin, such as a furuncle. Bacteriemia or septicemia may result and lead to localization in one or many bones. When bacteriemia becomes septicemia abscesses may occur in various organs of the body as well as in the osseous tissues. The prognosis for recovery without the development of chronic osteomyelitis is not as favorable in the child over three years of age as it is in the infant patient.

The treatment of acute osteomyelitis by means of various sulfonamide compounds has been of proved value. However, some patients have been found sensitive to the sulfonamides and in others the infecting organism was sulfa-resistant. Many patients so treated, with apparent success, subsequently developed sinuses and required surgery for the removal of sequestra or partial ostectomy for drainage of bone abscesses. Although the value of penicillin in the treatment of infections of bones following compound fractures, paranasal sinus suppuration, and in chronic osteomyelitis has been fairly well-established, few case reports of its use in acute hematogenous osteomyelitis have been made.

In each of the 12 cases which we are reporting, the acute infection was controlled by the use of penicillin, or a combination of penicillin and sulfonamides. In none of the 12 cases was surgery resorted to during the acute

illness after beginning penicillin therapy. Two of the 12 patients had been subjected to surgery prior to the administration of penicillin, and three were subsequently operated upon: one for the removal of a small sequestrum, a second, for removal of a sequestrum and later drainage of a small abscess, and a third, for the drainage of an abscess. These operations were performed months after the acute illness. All of the patients have been under observation for a period of five months or longer. Of the 12 patients included in this study, the youngest was just over three years of age and the oldest were two patients 12 years of age.

The focal infections included four femora, three tibiae, one humerus, one ischium, one cuneiform bone of the foot, one patella and femur, and one calvarium. In the latter case, however, the patient had been treated 15 months before for acute, hematogenous osteomyelitis of the left femur by means of sulfathiazole. In spite of this treatment, which was combined with surgery for drainage, several new foci appeared during the succeeding 12 months. The osteomyelitis of the skull, which represented a new focus, was successfully treated with penicillin, after obtaining a blood culture which was positive for *hemolytic Staphylococcus aureus*. The acute lesion in the skull healed without requiring surgical drainage. No new lesions which produced clinical symptoms appeared from October, 1943, to July 25, 1944, at which time the child was examined and found to be entirely well. The 12 cases which make up this report represent all of the acute hematogenous osteomyelitis patients which were admitted to our service, or seen by us in consultation, at the Children's Memorial Hospital,* in Chicago, between July, 1943, and March 1, 1945.

CASE REPORTS

Case 1.—*Acute Osteomyelitis of Skull with Meningitis.*

R. C., born April 2, 1937, white, male, entered Children's Memorial Hospital, July 9, 1942, acutely ill and complaining of pain in the left leg. A diagnosis of acute osteomyelitis of the left femur was made and treatment with sulfathiazole was started. July 16th, the abscess was drained and a hip spica was applied. Between July 16th and August 19th, 1943, the patient had new foci develop in the left ulna, right sacrum, and left humerus.

On October 18th, he complained of a severe headache, dizziness and vomiting. When he was examined at the Children's Memorial Hospital two days later he was found to be acutely ill, with a red pharynx, a markedly rigid neck, and a red tender area over the frontal bone. The spinal fluid was cloudy, the Pandy test was three plus, there were 4,000 cells, chiefly polymorphonuclear leukocytes, in each cubic centimeter, and gram-positive organisms. Roentgenograms showed osteomyelitis of the left frontal region of the skull. Both the blood culture and spinal fluid culture were positive for *hemolytic Staphylococcus aureus* organisms.

Twenty-five thousand units of penicillin in 500 cc. of normal saline solution were given intravenously at the rate of 15 drops per minute throughout the first day. Penicillin was then administered intramuscularly every three hours. Recovery was uneventful and healing complete.

*We are indebted to both the Medical and Surgical Services of the Children's Memorial Hospital and especially to Dr. Stanley Gibson, Chief of Staff, for the privilege of observing patients under their care and of following the course of the disease.

The patient was last seen on November 28, 1944. The lesions had remained healed, and there have been no recurrences.

A total of 500,000 units of penicillin was used in the treatment of this case.

Case 2.—*Acute Osteomyelitis of the Right Femur.*

R. G., born December 23, 1940, white, male, entered Children's Memorial Hospital December 21, 1943. Following an upper respiratory infection he had begun complaining of pain in the right arm, right chest, and subsequently the right thigh and leg. Physical examination revealed a slender, well-developed child, who was not acutely ill. Minimal swelling and redness were present in the right thigh. There was limitation of internal and external rotation of the hip. Blood culture was positive for *Staphylococcus aureus.* Roentgenograms confirmed the impression of osteomyelitis of the femur (Fig. 1). Sulfathiazole grains 7.7 every four hours was started. On December 27th, the temperature was still high and swelling in the right thigh had increased. Sulfathiazole was discontinued and penicillin was started (Fig. 2). There was a good response to this treatment. However, the destruction of bone made it advisable to protect the femur and, on January 22, 1944, a hip spica plaster encasement was applied. On January 12, 1945, nearly a year after the acute illness, a small sequestrum was removed. Prompt healing followed. March 31, 1945, a small fluctuant area in the scar was incised and a moderate amount of purulent material was expressed. The general health and physical condition of this patient is now satisfactory, and the local lesion has remained healed.

A total of 495,000 units of penicillin was used in the treatment of this case.

Case 3.—*Acute Osteomyelitis of the Right Humerus.*

D. D., born April 8, 1932, white, male, became ill on May 7, 1944. On the following day he complained of pain in his shoulder. During the next few days he became progressively more septic, with restlessness, and at times delusions.

He was seen at Children's Memorial Hospital on May 12th, and was found to have a swollen, painful right shoulder. The blood culture was positive for *Staphylococcus aureus.* Sulfathiazole, grains 7.7, every four hours was administered for two days. On the seventh day of the illness penicillin, 10,000 units intramuscularly every three hours, was started and four days later the dose was increased to 25,000 units every four hours. An encasement to splint the arm was applied on June 1st (20th hospital day) (Figs. 3 and 4).

The patient was last seen on April 5, 1945. There were no sinuses or deformities of the arm, and function was normal in every respect.

A total of 2,310,000 units of penicillin was used in the treatment of this case.

Case 4.—*Acute Osteomyelitis of the Right Femur.*

J. T., born September 20, 1932, white, male, entered Children's Memorial Hospital on May 24, 1944. May 19th he had developed pain in both his legs and his ankles had become swollen and painful. On May 31st, swelling and tenderness were marked over the distal third of the right femur. Roentgenograms showed a destructive process just proximal to the distal right femoral epiphysis. Swelling and tenderness persisted and the knee became held in 90 degrees of flexion. Twenty thousand units of penicillin were administered intramuscularly every four hours. Clinical improvement was rapid.

A total of 840,000 units of penicillin was used in the treatment of this case. Recovery was complete.

Case 5.—*Acute Osteomyelitis of the Right Upper Femoral Metaphysis.*

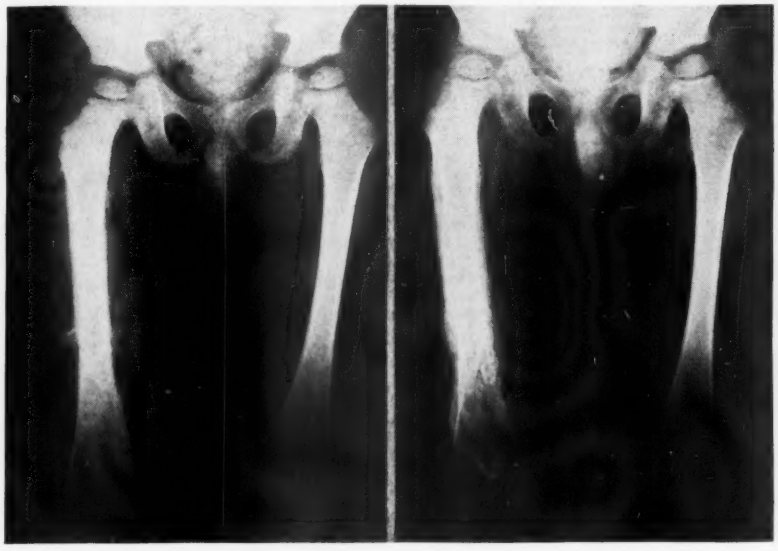
A. M., born September 9, 1933, white, female, entered Children's Memorial Hospital, July 4, 1944, with the complaint of severe pain in the right hip on weight-bearing. There was swelling of the right hip region, inability to rotate the hip, and tenderness posteriorly over the trochanter and the inguinal region. A sulfonamide drug had been administered by the family physician for three days prior to coming to the hospital. Blood culture showed no growth. Roentgenograms showed very slight bone destruction in the region of the greater trochanter (Fig. 5). The right leg was placed in Buck's

traction, and 100,000 units of penicillin per day were given. Recovery was uneventful (Fig. 6).

A total of 1,360,000 units of penicillin was used in the treatment of this case.

Case 6.—*Acute Osteomyelitis of the Right Ischium.*

D. M., born January 2, 1934, white, male. A furuncle was noted on the medial aspect of the left knee July 6, 1944. On July 10th he began to limp, the temperature was 103° F., and the following day 105° F. A physicnan prescribed a sulfonamide drug. There was no improvement, and July 20th he was brought to the Children's Memorial Hospital. Roentgenograms revealed osteomyelitic involvement of the right ischial bone (Fig. 7). Blood culture showed *nonhemolytic Staphylococcus.* Bone destruction continued (Fig. 8). Five doses, 20,000 units each, of penicillin were given intramusculary every 24 hours.



A B

A. 17th day after admission. B. 30th day after admission.

FIG. 7.—Case 2: R. G.: Roentgenograms showing the extensive destruction of the shaft of the femur.

An examination two months after discharge from the hospital showed the patient to be clinically normal.

A total of 1,020,000 units of penicillin was used in the treatment of this case.

Case 7.—*Acute Osteomyelitis of the Left Femur.*

LeR. B., born July 23, 1933, white, male, entered Children's Memorial Hospital, July 31, 1944, with the complaint of pain in his left thigh for five days. He had been unable to walk for four days and the evening temperature was high. Sulfathiazole was given for one day only. Penicillin was started, 12,500 units every three hours, and the recovery was rapid. On August 11, 1944, the penicillin was reduced to 6,000 units every three hours and was stopped on August 15, 1944. Changes in the architecture of the femur were minimal as shown in the roentgenograms. A small abscess developed four months later, in December, 1944, and this was operated upon January 15, 1945. *Staphylococcus aureus* was obtained in the culture of the abscess material. The wound healed promptly after the operation. The last examination was on April 5, 1945. The patient was then clinically well.

A total of 1,425,000 units of penicillin was used in the treatment of this case during the acute attack.

Case 8.—*Acute Osteomyelitis of the Right Tibia.*

W. S., born May 24, 1937, entered Children's Memorial Hospital on August 29, 1944. August 23rd a large boil on the left elbow had been lanced by the family physician. The right foot became very painful four days later, and he was not able to walk on it. His temperature was 102° F. He was given sulfonamides for two days, but the pain localized just above the ankle and he was admitted to Children's Memorial Hospital for treatment. Physical examination revealed a tender, red swelling in the distal third of the right leg. One hundred thousand units of penicillin were given intramuscularly every 24 hours for four days. Improvement was immediate and the penicillin was reduced to 80,000 units every 24 hours for the next six days, then 60,000 units every 24 hours for three days. Recovery was complete.

A total of 960,000 units of penicillin was used in the treatment of this case.

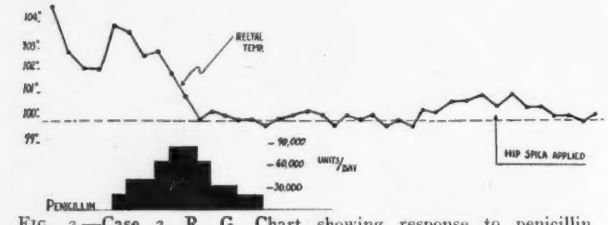


FIG. 2.—Case 2, R. G. Chart showing response to penicillin therapy.

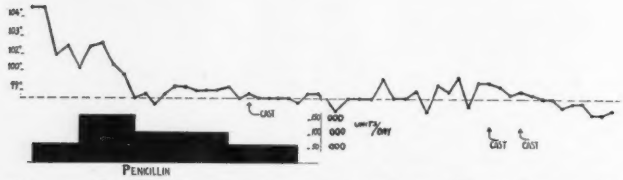


FIG. 3.—Case 3, D. D.: Chart of temperature (heavy line—rectal temperature) W. B. C., and penicillin (total units given per day).

Case 9.—*Acute Osteomyelitis of the Tarsal Bones of the Right Foot.*

M. G., born October 18, 1936, white, female, complained October 12, 1944, of pain in the right foot upon weight-bearing. October 18, 1944, she developed a septic temperature. Sulfathiazole was begun and continued until admission to Children's Memorial Hospital. October 23rd there was a fluctuating mass, and the abscess was opened.

She was transferred to Children's Memorial Hospital December 5, 1944. The right foot was red, swollen, and there were four or five draining sinuses. Her rectal temperature on admission was 100.4° F. Penicillin, 12,500 units intramuscularly every three hours, was started December 6th and continued for 17 days. Sulfathiazole, which had been stopped upon admission, was started again December 7th and continued for 16 days. Culture of the draining sinus and blood culture were positive for *Staphylococcus hemolyticus aureus.*

The clinical course was satisfactory. A sequestrectomy of the first cuneiform bone of the right foot was performed January 13, 1945, and the wound healed promptly.

When examined March 8, 1945, the wound was closed, and recovery was complete.

During the course of this disease the patient received approximately 141 Gm. of sulfathiazole before and 48 Gm. after her admission to Children's Memorial Hospital.

Case 10.—*Acute Osteomyelitis of the Left Lower Tibia.*

F. W., born June 10, 1940, white, male, complained of pain, and redness and swelling of the left ankle and foot were noted November 13, 1944. Sulfadiazine, 1 Gm. three times a day, was administered for one week. He was admitted to Children's Memorial

Hospital November 18. There was swelling, pain, and increased heat extending distally from the midtibia to the ankle and the dorsum of the foot. Blood culture showed no growth. A diagnosis of osteomyelitis of the left lower tibia was made. Penicillin, 100,000 units per day intramuscularly at three-hour intervals, was started and continued for ten days. On the third hospital day he received 3 Gm. of sulfathiazole. On the sixth hospital day he received a 150 cc. whole blood transfusion. Clinical improvement was satisfactory and on the 11th hospital day the dosage of penicillin was reduced to 10,000 units intramuscularly every four hours.

He was discharged on the 26th hospital day. The tenderness and swelling had disappeared. Motion and function of the ankle joint were normal.

The total amount of penicillin administered was 1,480,000 units.

FIG. 4.—Case 3, D. D.: This roentgenogram of June 20, 1944, the 39th day of hospitalization, shows the extent of the destructive process and the amount of involucrum formed.

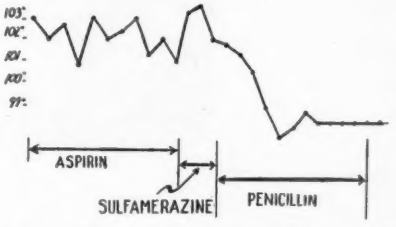


FIG. 5.—Case 4, J. T.: Chart of the hospital course and treatment.

Case 11.—*Acute Osteomyelitis of the Left Patella and Distal End of Femur.*

R. F., born March 15, 1939, white, male, was admitted to Children's Memorial Hospital January 17, 1945. His left knee was swollen, red, hot and tender. There was superficial venous engorgement over the thigh, and thickening over the metaphysis of the femur. Effusion into the knee joint was present. There was exquisite tenderness over the patella. Blood culture was not obtained. Sulfathiazole, 3 Gm. per day, was started upon admission, and on the first hospital day 15,000 units of penicillin every four hours was started. Sulfathiazole was discontinued on the 15th hospital day; penicillin was reduced on the tenth hospital day to 50,000 units intramuscularly each 24 hours, and was discontinued on the 16th hospital day.

He was last examined on April 12, 1945, and at that time was considered to be fully recovered.

This patient received 45 Gm. of sulfathiazole in 15 days and, concurrently, 1,300,000 units of penicillin.

Case 12.—*Acute Osteomyelitis of the Left Tibia.*

A. K., born January 14, 1934, white, male, complained of pain in the left ankle March 2, 1945, and his temperature was 105° F. He was admitted to Children's Memorial Hospital, March 3, 1945, and a diagnosis of osteomyelitis was made, although roentgenographic changes in the bone were still indefinite. One hundred thousand units of penicillin were administered intramuscularly each day in doses of 12,500 units every three hours for 11 days. He was discharged on the 13th hospital day.

When examined on April 12, 1945, he was entirely well.

The prognosis in the treatment of acute hematogenous osteomyelitis in childhood, as indicated by reports of various observers, was most discour-

aging prior to the development of chemical agents to which the organisms producing this disease have proved to be susceptible. Too frequently surgery was resorted to without first preparing the patient by a program of rest, blood transfusions, and correction of the body fluid balance. Extensive surgical procedures were occasionally recommended and instituted when the patient was critically ill, and these no doubt increased the mortality rate. Dickson[1] states that the average mortality "as nearly as can be determined in

FIG. 6.—Case 4, J. T.: Roentgenogram of the femur made 27 days after admission to Children's Memorial Hospital.

the usual type of the disease is somewhere around 10 to 15 per cent. The mortality in the septicemic type is well over 50 per cent; perhaps higher."

The results of penicillin therapy in a few reported cases,[2, 3, 4] and in this series of 12 consecutive cases of acute hematogenous osteomyelitis have included no deaths; no extensive areas of chronic osteomyelitis; and no instance of multiple foci in the bones after such treatment had been started. Three of these patients were critically ill, and in five of the patients (Cases 1, 2, 3, 6 and 9) blood cultures were positive for *Staphylococcus aureus*. *Hemolytic Staphylococcus aureus* was also cultured from the spinal fluid of Case 1. Negative blood culture in other cases may be attributed, in part, to the length of the elapsed time between onset and admission to Children's Memorial Hospital, and, in part, to sulfonamides which had already been administered.

The question of whether or not initial drainage should be carried out in each case of acute hematogenous osteomyelitis is still a controversial issue. Dickson[1] favors early drainage of the osseous focus except in the fulminating type. Wilson and McKeever,[5] as well as Dickson, reported that patients

treated with the sulfonamides without initial drainage frequently had more bone destruction and required greater surgical interference later than did those cases in which surgical drainage was instituted during the acute stage of the disease. The response to penicillin therapy in the short series of cases which we are reporting encourages us in the opinion that penicillin will prove to be a more effective chemotherapeutic agent for this disease than were the sulfonamides.

In the short series of cases reported here, sulfonamides had proved to be

FIG. 7.—Case 6, D. M.: Roentgenogram of July 27, 1944. (17th day of illness).

of little value in those cases in which they were employed before penicillin was started. Almost immediate response to penicillin therapy was noted in the rapid lowering of the temperature of the acutely ill patients. The failure of the disease to spread to other bones or other organs in any of our patients, encourages us to hope that if penicillin could be started immediately after the onset of the acute illness, abscess formation, spread of infection in the bone that is involved, or devitalization of bone and the formation of sequestra may become relatively uncommon sequelae of acute osteomyelitis in children. Late surgery, which has been necessary for the removal of sequestra or the drainage of bone abscesses, may be rarely necessary. Since the bacterial organisms which produce more than 95 per cent of the cases of acute hematogenous osteomyelitis in children are susceptible to penicillin, while some of them are resistant to the sulfonamides, the use of penicillin should be a *must* when this disease is diagnosed.

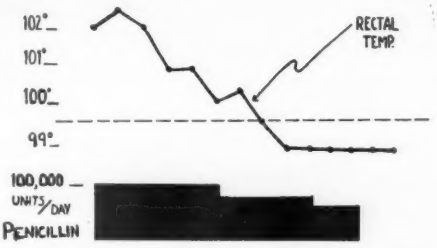


FIG. 8.—Case 6, D. M.: The above chart is the hospital summary of this case.

CONCLUSIONS

1. Twelve cases of acute hematogenous osteomyelitis in children, age three to 12 years, have been studied and reported.

2. Penicillin was employed successfully in the treatment of each of the 12 patients.

3. The infection in ten of the patients treated successfully by penicillin had proved to be resistant to the sulfonamides.

4. Surgery was necessary in four of the 12 patients: in one, for the removal of a small sequestrum, and in three, for the drainage of an abscess after the acute infection had subsided.

5. Penicillin appears to be a more effective agent in the treatment of acute hematogenous osteomyelitis than has any other therapeutic agent, including the sulfonamides.

6. Early use of penicillin in adequate doses administered at frequent intervals may not only cure the initial infection but prevent spread to other bones and in a majority of cases make surgery unnecessary.

7. If the penicillin is not started until after a bone has been extensively damaged, with necrosis of segments of cortex, central destruction of bone, and cavity formation, late surgery may become necessary.

8. From our experience in this short series of cases, we hazard the suggestion that in children, age three to 12 years, acute hematogenous osteomyelitis may be effectively treated if penicillin is administered intramuscularly in doses of 15,000 to 20,000 units each every three hours day and night. After the temperature begins to subside, the size of each dose may be reduced to 10,000 units, but the frequency of dosage must be maintained. When the patient becomes afebrile the dosage may be reduced gradually and discontinued after five days of normal temperature. Recurrences may occur if penicillin is stopped too soon. In several cases, there was a small, secondary temperature rise after stopping the penicillin.

9. While making use of a remarkable chemotherapeutic agent such as penicillin, we must not neglect to use well-established principles of medical care, such as the maintenance of the fluid balance of the body through the administration of normal salt solution, glucose, plasma or blood. Splints, plaster encasements or traction should be used when they are needed for supporting the diseased bone or to prevent contractures.

REFERENCES

[1] Dickson, Frank D.: The Clinical Diagnosis, Prognosis and Treatment of Acute Hematogenous Osteomyelitis. J. A. M. A., **127**, 212–216, January 27, 1945.

[2] Feierabend, F. L.: Staphylococcus Osteomyelitis: A Case Report. J. Kansas Med. Soc., **45**, 200, June, 1944.

[3] Herrell, W. E., and Nichols, D. R., and Heilman, D. H.: Penicillin, Its Usefulness, Limitations, Diffusion and Detection: With Analysis of 150 Cases in which it was Employed. J. A. M. A., **125**, 1003, August 12, 1944.

[4] Riddell, T.: Penicillin in Acute Osteomyelitis: Report of a Case. Nebraska Med. J., **29**, 284, September, 1944.

[5] Wilson, J. C., and McKeever, F. M.: Hematogenous Acute Osteomyelitis in Children. J. Bone & Joint Surg., **18**, 328–332, April, 1936.

BLOOD IODINE STUDIES*

VII. THE RELATION OF THE BASAL METABOLIC RATE TO THE BLOOD IODINE IN THYROID DISEASE

GEORGE M. CURTIS, M.D., AND M. BEEN FERTMAN, M.D.
COLUMBUS, OHIO

FROM THE DEPARTMENT OF RESEARCH SURGERY OF THE OHIO STATE UNIVERSITY, COLUMBUS, OHIO.

VARIOUS PATHOLOGIC PROCESSES, as well as changing physiologic states, produce deviations in the metabolism of the human body. These are reflected in the basal metabolic rate. Most important in this regard are the various diseases of the thyroid gland, an organ which plays an important, if not a dominant, rôle in setting the pace at which the body's myriad cells function. It is common clinical knowledge that the basal metabolic rate is decreased with diminution of thyroid activity, falling as low as minus 40 per cent in patients with total myxedema. Plummer and Boothby[1] found that the daily rate of thyroxine decay ranges between 0.2 and 0.4 mg. Thus, a therapeutic daily dose of from 0.3 to 0.4 mg. of thyroxine is necessary to maintain a normal basal metabolic rate in wholly myxedematous patients at bed rest.[2]

THE BASAL METABOLIC RATE IN THYROID DISEASE

The basal metabolic rate varies with the type of goiter. Boothby[3] found the average basal metabolic rate in 254 patients with nontoxic goiter to be plus 2 per cent. The distribution of basal metabolic rates in 1,111 patients with nodular goiter, without hyperthyroidism, was similar to that found in normal individuals.[4] On the other hand, the average basal metabolic rate was plus 30 per cent in 366 patients with toxic nodular goiter,[3] and exceeded plus 20 per cent in 93 per cent of 2,569 patients with exophthalmic goiter.[4] The average basal metabolic rates which we have obtained in similar but smaller groups agree well with those of Boothby (Table I). In all patients having goiter with hyperthyroidism, the rates are significantly elevated, along with the whole blood iodine. Although less increased, the basal metabolic rate in patients with nontoxic nodular goiter is nevertheless significantly higher than normal. In all goitrous conditions studied, as well as in thyroid malignancy, the variation in basal metabolic rates among patients exceeds that among normal persons.

In Table II is shown a comparison of the distribution of the basal metabolic rates in four different thyroid diseases with that in normal individuals. As in a similar study of the blood iodine distribution,[6] *arbitrary* limits are chosen on the basis of the standard deviation for normal persons. The distribution of values in the normal 1 s.d.* and 2 s.d. limits varies considerably and thus accounts, at least in part, for the differences found in the

* Aided by a grant from the Comly Fund for Research of the Ohio State University.

* 1 s.d. = one times the standard deviation, *etc.*

average basal metabolic rate of each group. The deviation from normal is most marked in patients with hyperthyroidism (toxic nodular and exophthalmic goiter) in which almost 90 per cent of all values exceed the normal plus 2 s.d. limit, plus 11 per cent, and no values are below the minus 1 s.d. limit, minus 13 per cent.

TABLE I

AVERAGE BASAL METABOLIC RATE AND WHOLE BLOOD IODINE CONCENTRATION IN VARIOUS THYROID DISEASES

(+ − *the Standard Error*)

Clinical Condition	Basal Metabolic Rate No.	Basal Metabolic Rate Mean + − Standard Error	Blood Iodine‡ (Micrograms %) No.	Blood Iodine‡ (Micrograms %) Mean + − Standard Error
Hypothyroidism	77	−16±1*	66	3.6±0.1
Normal	46	− 5±1	39	4.2±0.2
Nontoxic diffuse colloid goiter	14	− 7±2	9	4.4±0.3
Nontoxic nodular goiter	72	+ 1±1†	44	3.9±0.2
Toxic diffuse colloid goiter	6	+26±9†	3	6.4±0.7†
Toxic mixed goiter	4	+26±5†	4	7.2±1.1†
Toxic nodular goiter	54	+28±2†	29	7.9±0.8†
Exophthalmic goiter	73	+39±3†	41	9.3±0.6†
Carcinoma of the thyroid	11	+16±5*	9	4.8±0.7
Chronic thyroiditis	3	−12±5	3	5.2±0.9

* Significantly different from the normal average.

† Highly significantly different from the normal average.

‡ Chromium-trioxide method of blood iodine determination.[5]

TABLE II

PERCENTAGE DISTRIBUTION OF THE BASAL METABOLIC RATES IN THE NORMAL 1 S.D. AND 2 S.D. LIMITS

(*Normal Average Basal Metabolic Rate* + − *the Standard Deviation* = −5±8%)

Clinical Condition	No.	Range of Values (%)	Percentage Distribution of Basal Metabolic Rates: Below −2 s.d. (Below −21%)	−2 s.d. to −1 s.d. (−21 to −13%)	−1 s.d. to Aver. (−13 to −5%)	Average to +1 s.d. (−5 to +3%)	+1 s.d. to +2 s.d. (+3 to +11%)	Above +2 s.d. (Above +11%)
Hypothyroidism	77	−37 to +1	23%	46%	21%	10%	0%	0%
Normal	46	−19 to +21	0%	11%	39%	39%	4%	7%
Nontoxic nodular goiter	72	−23 to +35	1%	4%	26%	28%	20%	21%
Toxic nodular goiter	54	−17 to +69	0%	1%	0%	6%	6%	87%
Exophthalmic goiter	73	−9 to +100	0%	0%	1%	4%	8%	87%

An opposite tendency is found in hypothyroidism, with nearly 70 per cent of all basal metabolic rates below the 1 s.d. range and none above. In nontoxic nodular goiter the distribution shows a beginning shift toward higher values, with as many as 41 per cent of the basal metabolic rates above the plus 1 s.d. limit and half of these above the plus 2 s.d. limit. A comparison of the distribution of the basal metabolic rates with that of the whole blood in thyroid disease shows that *the basal metabolic rate alone more frequently indicates the presence of thyroid disease than does the unfractionated whole blood iodine* (Table III).

The similarity in distribution of basal metabolic rates within the described limits in toxic nodular goiter and in exophthalmic goiter is misleading without a consideration of the values exceeding the normal plus 2 s.d. limit. Such

values are higher in exophthalmic goiter than in toxic nodular goiter, attaining a maximum in the groups considered here of plus 100 per cent in exophthalmic goiter and of plus 67 per cent in toxic nodular goiter (Table II). This accounts for the significant difference in the average basal metabolic rates in exophthalmic goiter, plus 39 per cent, and in toxic nodular goiter, plus 28 per cent. A corresponding significant difference could not be demonstrated in

TABLE III

A COMPARISON OF THE DISTRIBUTION OF BASAL METABOLIC RATES AND WHOLE BLOOD IODINE VALUES IN THE NORMAL 1 S.D. AND 2 S.D. LIMITS

Clinical Condition	Below −2 s.d.	Within the 1 s.d. Limits	Within the 2 s.d. Limits	Above +2 s.d.
Hypothyroidism:				
Whole blood iodine	5%	70%	93%	2%
Basal metabolic rate	23%	31%	77%	0%
Normal:				
Whole blood iodine	0%	68%	97%	3%
Basal metabolic rate	0%	68%	93%	7%
Nontoxic nodular goiter:				
Whole blood iodine	1%	66%	92%	7%
Basal metabolic rate	1%	54%	78%	21%
Toxic nodular goiter:				
Whole blood iodine	0%	34%	55%	45%
Basal metabolic rate	0%	6%	13%	87%
Exophthalmic goiter:				
Whole blood iodine	0%	20%	37%	63%
Basal metabolic rate	0%	5%	13%	87%

the average unfractionated whole blood iodine values of these groups, 9.3 and 7.9 micrograms per cent, respectively[6] (Table I). More data, especially on *fractionated* blood iodine, might reveal a significant difference.

Werner[7] attributes the relatively lower basal metabolic rate found in nodular goiter to a slower and more gradual onset of the hyperthyroidism than in exophthalmic goiter. Whether this difference between the basal metabolic rates in these two forms of goiter with hyperthyroidism is actually due to a difference in the rapidity with which toxic symptoms become manifest or to other factors inherent in these diseases, we shall not discuss at this time. Our own studies also indicate that the onset of hyperthyroid symptoms is slower in nodular than in exophthalmic goiter. Hyperthyroid symptoms sufficiently severe to bring the patient to a physician took an average of 3.2 years to develop in our group of patients with toxic nodular goiter, and 1.4 years, or about half that time, in those with exophthalmic goiter.

In four patients with toxic mixed goiter and in six with toxic diffuse colloid goiter, the average basal metabolic rates are again lower than those found in exophthalmic goiter. Nevertheless, the average duration of hyperthyroid symptoms in the few with toxic mixed goiter approximates that in exophthalmic goiter, while the duration of these symptoms in those with toxic diffuse colloid goiter is equal to that in toxic nodular goiter. The average basal metabolic rate is plus 26 per cent both in toxic mixed and toxic diffuse colloid goiter, and agrees closely with the average basal metabolic rate in

toxic nodular goiter, in our series plus 28 per cent, as well as in Boothby's[3] series, plus 30 per cent (Table I).

The *average* basal metabolic rate in 72 patients with nontoxic nodular goiter, plus 1 per cent, is significantly greater than in a group of normal individuals from this region, minus 5 per cent, yet is far less than the average basal metabolic rate in toxic goiter. As many as 21 per cent of the basal metabolic rates in the group with nontoxic nodular goiter exceed the normal plus 2 s.d. limit, plus 11 per cent (Table II). A lower average metabolism is found in simple diffuse colloid goiter. The average is minus 7 per cent and does not differ significantly from the normal (Table I). However, the group is relatively small, comprising only nine patients, all young persons.

In carcinoma of the thyroid there are several factors involved which may exert their effects, singly or in combination, upon the body metabolism. If the carcinoma is locally extensive, one might even expect a much reduced basal metabolic rate because of massive destruction of thyroid tissue. In partial replacement of the normal gland, on the other hand, there may be compensatory overfunctioning of the remaining cells, in varying degrees. In addition to these factors, the type of thyroid abnormality present prior to the development of the carcinoma may also be reflected in the basal metabolic rate. We have postulated in a previous paper[6] that the level of the blood iodine may depend more upon the nature of the thyroid gland in which the malignancy arises than upon the character of the malignancy itself. However, this again would be influenced, as in the case of the basal metabolic rate, by the extent of destruction of functioning thyroid tissue and the degree of resultant overcompensation by the remaining normal cells.

In carcinoma of the thyroid we have, in addition to the thyroid activity present, another factor which may be reflected in the basal metabolic rate. This is the process of malignancy itself. Unlike the level of the blood iodine,[8] the basal metabolic rate is in general increased by malignant neoplastic disease.[4, 9] Thus, moderate elevation of the average basal metabolic rate in 11 patients with carcinoma of the thyroid, plus 16 per cent, may be consistent with the degree of increase one might expect to find in most malignant disease. As can be gleaned from the work of Boothby and Sandiford,[4] the percentage of basal metabolic rates exceeding plus 20 per cent is almost the same in malignancy of the thyroid as in certain other malignant neoplastic disease, the values being plus 22 and 20 per cent, respectively.

BASAL METABOLIC RATE AND WHOLE BLOOD IODINE IN THYROID DISEASE

Unlike thyroid disease, other endocrine disturbances are not so consistently reflected in the basal metabolic rate. Findings of the basal metabolic rates in these nonthyroid diseases[9, 10] suggest that the values frequently do not parallel the *hypo* and *hyper* states of the glands involved.[10] Moreover, thyroid disease differs from nonthyroid disease in the corresponding general changes observed in the basal metabolic rate and the level of the blood iodine, particularly of the various forms of "organic iodine."[12–14]

It appears to be the increased protein-bound fraction of the blood iodine, and more particularly its thyroxine-containing portion, which is related to the increased basal metabolic rate of hyperthyroidism.[15, 16] In a series of 100 patients with suspected thyroid disturbances and of ten control individuals, Salter, and his associates,[11] found that when the clinical diagnosis and basal metabolic rate are in agreement, there is close parallelism between the plasma protein-bound iodine and the basal metabolic rate. Of 29 per cent who did not show such a relationship, the plasma protein-bound iodine proved more reliable as an index of the clinical status than did the basal metabolic rate, particularly in "Graves' disease without hyperthyroidism."

Further, the similar response of both the basal metabolic rate and the blood iodine to thyroid therapy suggests again an association of these factors. Thus, for example, in the treatment of myxedema with thyroxine,[17] or with thyroid gland,[13] the basal metabolic rate and the protein-bound blood iodine rise, while in hyperthyroidism treated with inorganic iodine, the "organic" level of blood iodine usually declines with the basal metabolic rate.[18] The recent investigations of thiouracil therapy in hyperthyroidism reveal that with this drug, too, the drop in basal metabolic rate, as well as the alleviation of symptoms,[19, 20] is accompanied by a drop in the protein-bound iodine of the blood.[20]

In a study of 18 children, from two to 13 years of age, Macciotta found no constant relation between the blood iodine and the basal metabolic rate, either in the group as a whole or in the same individual. From these findings he concludes that other factors besides the thyroid must be important in the iodine metabolism of children.[21] K. B. Turner, and his associates,[22] could find no correlation between the total blood iodine and the basal metabolic rate in 20 patients with hyperthyroidism, in five with nontoxic nodular goiter and in two with thyroiditis, as well as in patients with hypertensive vascular disease or with leukemia.

In 1935, Mobius and Nolte[23] observed a sharp parallelism between the increased basal metabolic rate and the per cent rise in blood iodine in untreated hyperthyroidism. In 1938, Gerda Bülmann[13] noted that the graphic relationship between the alcohol fractionated "protein-bound" iodine in Graves' disease and the basal metabolic rates, ranging from plus 80 to plus 180 per cent, resembled a logarithmic curve. Empirically, through various combinations of the data, she found the best equation describing the relationship to be: Per cent B.M.R. $-$ 29 $=$ 100 log (micrograms per cent iodine). From her findings she concluded that a relatively greater amount of circulating thyroid hormone is required to maintain a high metabolism; also, that a departure from a normal basal metabolic rate does not occur without change in the "protein-bound" iodine.

Salter[24] was able to demonstrate a highly significant correlation between the blood iodine and the basal metabolic rate, on data for which Elmer and Scheps[25] could find no parallelism, by using a logarithmic relationship:

B.M.R. = log (blood iodine —3), in which 3 is an arbitrary constant roughly representing the amount of inorganic iodine in the blood. His data included small groups of hyperthyroid patients, euthyroid normal individuals, euthyroid goiter patients, euthyroid individuals with low basal metabolic rates and hypothyroid patients. Salter[24] states that it can be inferred that the blood iodine and the basal metabolic rate are related: if the clinical classification is adequate; the analytical technic good; the exogenous iodine intake low; and a steady physiologic state is attained before the blood is drawn for analysis.

In a study of 373 mixed cases, with basal metabolic rates ranging from minus 30 to plus 50 per cent, McClendon and Foster[14] found a significant linear correlation between the basal metabolic rate, denoted in calories per sq. m. per hr., and the "thyroxin" iodine, a fraction which is nonextractable with methyl alcohol followed by acetone. The correlation coefficient thus obtained was +0.627.

In considering the total blood iodine, the basal metabolic rate and other factors in a series of different physiologic and pathologic conditions, we have found that the average unfractionated blood iodine is not invariably elevated in those conditions in which the basal metabolic rate is elevated.[6, 8, 9] Likewise, the average basal metabolic rate does not necessarily correspond to an increase in the level of the blood iodine. In all forms of toxic goiter, both are abnormally high (Table I). On the other hand, the moderate elevation in average basal metabolic rate which may occur in nontoxic nodular goiter is not accompanied by a corresponding increase in the blood iodine (Tables I and III). Likewise, a parallelism between increased metabolism and level of the blood iodine may be absent in carcinoma of the thyroid (Table I). In hypothyroidism the basal metabolic rate may be reduced out of proportion to the level of the average unfractionated blood iodine, perhaps due to a history of iodine medication in such patients or to the inclusion of patients with other hypometabolic disturbances in this group (Tables I and III).

In an analysis of covariance, including a total of 11 euthyroid (151 individuals) and eight different thyroid conditions (200 patients), we could not demonstrate a single relationship between the whole blood iodine and the basal metabolic rate which would similarly describe all. Significant correlations between the unfractionated blood iodine and the basal metabolic rate were found only in disease of thyroid origin. These included nontoxic nodular goiter, toxic nodular goiter and exophthalmic goiter, all groups in which there was a relatively large number of individuals (Tables IV and V). The association between the blood iodine and the basal metabolic rate in these three diseases was further corroborated by significant multiple correlation coefficients indicating some probable relationship of the blood iodine with the basal metabolic rate to the duration of symptoms of the disease, as well as to the age of the patient (Table V).

We[5] could demonstrate a significant correlation between the basal metabolic rate and the unfractionated blood iodine in 64 patients with hypothyroidism,

whose whole blood iodine was determined by the chromium trioxide method. This may be due to the same factors responsible for a normal average blood iodine in this group,[6] such as the inclusion of patients who may have received iodine medication, or of those with forms of hypometabolism other than actual hypothyroidism. A heterogeneity among the patients with hypothyroidism is further suggested by the finding of significant correlations between

TABLE IV

CORRELATION COEFFICIENTS OF BASAL METABOLIC RATE AND WHOLE BLOOD IODINE IN 19 DIFFERENT CLINICAL CONDITIONS

Clinical Condition	Number of Individuals	Correlation Coefficient
Euthyroid:		
Normal	34	+0.153
Functional disturbances	25	−0.336
Psychoneurosis	17	+0.237
Obesity	15	−0.207
Menopause	12	+0.284
Hypertension	12	+0.115
Arthritis	10	+0.108
Hypometabolism	9	+0.141
Migraine	9	−0.209
Hirsutism	5	−0.338
Diabetes mellitus	3	−0.388
Thyroid:		
Hypothyroidism	64	+0.148
Nontoxic diffuse colloid goiter	7	+0.240
Nontoxic nodular goiter	44	+0.376*
Toxic diffuse colloid goiter	3	+0.254
Toxic mixed goiter	4	+0.823
Toxic nodular goiter	29	+0.548†
Exophthalmic goiter	40	+0.444†
Carcinoma of the thyroid	9	−0.151

* Significant correlation.
† Highly significant correlation.

TABLE V

SIGNIFICANT CORRELATION COEFFICIENTS. RELATIONSHIP OF WHOLE BLOOD IODINE, BASAL METABOLIC RATE, DURATION OF SYMPTOMS AND AGE OF PATIENT

	Correlation Coefficient of Blood Iodine, B.M.R.		Multiple Correlation Coefficient of Blood Iodine, B.M.R.	
Thyroid Disease	Linear Relation	Logarithmic Relation	Duration of Symptoms	Age of Patient
Toxic nodular goiter	+0.548†	+0.563†	+0.569†	+0.555†
Exophthalmic goiter	+0.444†	+0.454†	+0.450†	+0.449†
Nontoxic nodular goiter	+0.376*	+0.330*	+0.396*	+0.427*
Hypothyroidism‡:				
6 males	+0.833*	+0.868*	.....	.....
7 females	.....	.....	.....	+0.986†

* Significant correlation.
† Highly significant correlation.
‡ Explained in text.

the basal metabolic rate and the whole blood iodine only when males and females were considered separately in another smaller group of hypothyroid patients (Table V), whose blood iodine was determined by the dry ash technic.[26]

Further correlation between the basal metabolic rate and the blood iodine

should be expected since a part, at least, of the blood iodine appears to represent the circulating thyroid hormone. Also, significant correlation coefficients might be found in other clinical conditions, besides those in which we were able to demonstrate them, when the "organic" fraction of the blood iodine is contrasted with the basal metabolic rate, especially in larger groups of individuals.

In our analysis of covariance we were unable to find any significant departure of the whole blood iodine-basal metabolic rate relationship from linearity in those diseases in which a significant correlation between these two factors was found. Moreover, using the logarithmic relationship, with or without constants, we found that the correlation coefficients thus obtained in each of the 19 conditions (11 euthyroid and eight thyroid) investigated did not differ significantly from those obtained on a linear basis. Likewise, the logarithmic equation did not better describe a single relationship between the blood iodine and basal metabolic rate which would hold for all 19 considered as a whole.

SUMMARY

1. In all forms of toxic goiter, the average basal metabolic rate is elevated. However, it is more increased in exophthalmic goiter than in any other form of goiter with hyperthyroidism, despite a similarity in the extent of increase of the average unfractionated whole blood iodine in all forms of toxic goiter, with or without exophthalmos.

2. Although lower than the average basal metabolic rate found in toxic goiter, those of 72 patients with nontoxic nodular goiter were significantly higher than normal. This moderate increase in the average was unaccompanied by any average increase in the whole blood iodine.

3. The moderate elevation of the average basal metabolic rate in 11 patients with carcinoma of the thyroid may be consistent with the degree of increase one might expect to find in most malignant disease. On the other hand, it may be the result of various factors including the nature of the thyroid gland in which the carcinoma develops, the extent of destruction of functioning thyroid tissue and the degree of resultant compensation by the remaining cells, as well as the presence of malignancy *per se*.

4. Variation in the basal metabolic rates in different goitrous conditions was found to exceed such variation among normal individuals.

5. Significant positive correlation coefficients indicating a probable association between the basal metabolic rate and the whole blood iodine were demonstrated in nontoxic nodular, toxic nodular and in exophthalmic goiter. There was no significant deviation from linearity in any of these relationships.

6. An interrelationship between the whole blood iodine and basal metabolic rate with the duration of symptoms of the disease, as well as with the age of the patients, was indicated in all three of these diseases by significant multiple correlation coefficients.

7. The determination of the basal metabolic rate is a more reliable test

of thyroid activity than the level of the unfractionated whole blood iodine. However, both determinations, considered together, are superior to either alone.

BIBLIOGRAPHY

1 Plummer, H. S., and Boothby, W. M.: Specific Dynamic Action of Thyroxin. Am. J. Physiol., **55**, 295, 1921.
Plummer, H. S.: The Interrelationship of Function of the Thyroid Gland and of Its Active Agent, Thyroxin, in the Tissues of the Body. J. A. M. A., **77**, 243, 1921.

2 Thompson, W. O., McLellan, L. L., Thompson, P. K., and Dickie, L. F. N.: The Rates of Utilization of Thyroxine and of Desiccated Thyroid in Man: The Relation Between the Iodine in Desiccated Thyroid and Thyroxine. J. Clin. Investigation, **12**, 235, 1933.
Thompson, W. O., Thompson, P. K., Taylor, S. G., Nadler, S. B., and Dickie, L. F. N.: The Pharmacology of the Thyroid in Man. J. A. M. A., **104**, 972, 1935.

3 Boothby, W. M.: The Basal Metabolic Rate in Hyperthyroidism. J. A. M. A., **77**, 252, 1921.

4 Boothby, W. M., and Sandiford, I.: Summary of the Basal Metabolism Data on 8614 Subjects: With Especial Reference to the Normal Standards for the Estimation of the Basal Metabolic Rate. J. Biol. Chem., **54**, 783, 1922.

5 Matthews, N. L., Curtis, George M., and Brode, W. R.: Determination of Iodine in Biological Materials: Refinements of the Chromium Trioxide Oxidation Method. Ind. & Eng. Chem., **10**, 612, October 15, 1938.

6 Curtis, George M., and Fertman, M. Been: Blood Iodine Studies: VI. An Analysis of the Blood Iodine in Thyroid Disease. Arch. Surg., **50**, (4), 207, April, 1945.

7 Werner, A. A.: Endocrinology: Clinical Application and Treatment. Lea & Febiger, Philadelphia, 1937, 1942.

8 Curtis, George M., and Fertman, M. Been: Blood Iodine Studies: VIII. The Blood Iodine in Nonthyroid Disease. To be published.

9 Curtis, George M., and Fertman, M. Been: Blood Iodine Studies: IX. The Basal Metabolic Rate and its Relationship to the Blood Iodine in Nonthyroid Disease. To be published.

10 Engelbach, W.: Endocrine Medicine, Vol. 1, 1932, pp. 382-383, Baltimore, Maryland.

11 Salter, W. T., Bassett, A. M., and Sappington, T. S.: Protein-bound Iodine in Blood: VI. Its Relation to Thyroid Function in 100 Clinical Cases. Am. J. Med. Sc., **202**, 527, 1941

12 Davison, R. A., and Curtis, George M.: Acetone Fractionation of Blood and Urinary Iodine. Proc. Soc. Exper. Biol. & Med., **41**, 637, 1939.
Davison, R. A., Zollinger, R. W., and Curtis, George M.: The Fractionation of Blood Iodine: I. Findings in Patients with Normal Thyroid Function and with Hypothyroidism. J. Lab. and Clin. Med., **27**, 643, 1942.
Davison, R. A., and Curtis, George M.: Unpublished data.

13 Bűlmann, G.: Über den Blutjodspiegel: Seine Bestimmung und Seine Beziehung zum Grundumsatz Besonders Bei Myxoedem und Morbus Basedowi. Skand. Arch. f. Physiol., Suppl. No. **12**, p. 89, 1938. Univ. of Copenhagen.

14 McClendon, J. F., and Foster, W. C.: Thyroid Hormone in Blood and Tissues in Relation to Basal Metabolic Rate. Endocrin., **28**, 412, 1941.

15 Bassett, A. M., Coons, A. H., and Salter, W. T.: Protein-bound Iodine in Blood: V. Naturally Occurring Iodine Fractions and their Chemical Behavior. Am. J. Med. Sc., **202**, 516, 1941.

16 Salter, W. T., and Bassett, A. M.: A Physiological Interpretation of Blood Iodine Fractions in Terms of Thyroid Function (in 100 Cases), Tr. A. Am. Physicians, **56**, 77, 1941.

[17] Eppinger, E. C., and Salter, W. T.: The Daily Requirement in Human Hypothyroidism of Purified Human Thyroid Hormone at Various Metabolic Levels: A Comparison Between Spontaneous Myxedema and Cachexia Strumipriva. Am. J. Med. Sc., **190**, 649, 1935.

[18] Gutzeit, K., and Parade, G. W.: Blutjodstudien: V. Mitt. Die Beeinflussung des Jodspiegels durch Jod und Dijodtyrosin. Der Jodquotient in Bedeutung fur die Inkretlage. Ztschr. klin. Med., **133**, 533, 1938. Seiner.

[19] Astwood, E. B.: Treatment of Hyperthyroidism with Thiourea and Thiouracil. J. A. M. A., **122**, (2), 78, 1943.

[20] Williams, R. H., and Bissell, G. W.: Thiouracil in the Treatment of Thyrotoxicosis. New Eng. J. Med., **229**, (3), 97, 1943.

[21] Macciotta, G.: Sui vapporti Tra iodemia e metabolismo basale wei bambini. Acta. Paediat., **22**, 156, 1938.

[22] Turner, K. B., DeLamater, A., and Province, W. D.: Observations on the Blood Iodine: I. The Blood Iodine in Health in Thyroid and Cardiorenal Disease, and in Leukemia. J. Clin. Invest., **19**, 515, 1940.

[23] Mobius, W., and Nolte, F. A.: Verhalten von Grundumsatz und Blutjod bei Thyreotoxikosen. Ztschr. f. klin. Med., **128**, 174, 1935.

[24] Salter, W. T.: The Endocrine Function of Iodine. Cambridge, Mass., Harv. Univ. Press, 1940.

[25] Elmer A. W., and Scheps, M.: The Iodine Content of the Blood and of Urine and the Basal Metabolic Rate: Their Value in the Diagnosis of the Function of the Thyroid Gland. Acta Med. Scand., **82**, 126, 1934.

[26] Davis, C. B., and Curtis, George M.: Blood Iodine Studies: I. The Quantitative Determination of the Iodine Content of Blood. J. Lab. & Clin. Med., **18**, (1), 24, 1932.

[27] Phillips, F. J., and Curtis, George M.: Blood Iodine Studies: IV. The Clinical Determination of Iodine in Blood, Urine and Feces. Am. J. Clin. Path., **4**, 346, 1934.

VAGOTOMY FOR GASTRODUODENAL ULCER*

LESTER R. DRAGSTEDT, PH.D., M.D.
CHICAGO, ILL.
FROM THE DEPARTMENT OF SURGERY OF THE UNIVERSITY OF CHICAGO, CHICAGO, ILL.

A VOLUME to honor the 20 years of superb service that Dr. Dallas B. Phemister has given to the Department of Surgery and to the Medical School of the University of Chicago is fitting and appropriate. It is a great pleasure and a privilege for me to take part in this celebration, for I have been closely associated with him during all this time. We have worked together and what I have learned of surgery has come chiefly from him. He has taught best by example, and his modesty and industry, but best, his scientific integrity have set the standard, and this is chiefly responsible for the accomplishments of the Department. Sustained experimentation in the laboratory and honest observation and recording in the Clinic have constantly marked his way. Few men have done so well in both fields. Enthusiasm goes with him and the will to work. It is especially gratifying that this occasion looks upon him in the full flood of his powers and we hope that it will convey, even though faintly, our warm admiration and regard.

In previous papers[1] I have presented our early experience with surgical division of the vagus nerves in patients with gastroduodenal ulcer, together with brief descriptions of the operative technic involved. It is the purpose of this communication to survey the present status of this work and to refer to some studies in the laboratory that provide for the first time information concerning the relative importance of nervous and humoral factors in determining the volume and acidity of the gastric secretion.

The operation was undertaken because of the conviction, arrived at by experimental work on the lower animals, that pure gastric juice as it is secreted by the fundus of the stomach, has the capacity to destroy and digest various living tissues, including the wall of the jejunum, duodenum, and even the stomach itself.[2] It does not do this under normal conditions because the usual and appropriate stimulus to gastric secretion is the ingestion of food. This dilutes and neutralizes the gastric juice and decreases its corrosive powers. In normal man the secretion of gastric juice in the intervals between meals, when there is no food in the stomach or upper intestines, falls off to a small quantity that can be buffered by the saliva, pyloric mucus, and the regurgitated duodenal secretions. The chief secretory abnormality in ulcer patients lies not in the production of a juice with higher than normal acidity, nor even in the production of more normal juice in response to the usual stimuli, although there is some evidence that this occurs, but rather in the secretion of abnormally large amounts of gastric juice in the intervals between meals particularly at night when the stomach is empty and there is no obvious

* This work was done with the aid of a number of associates, including F. M. Owens, Jr., M.D., P. W. Schafer, M.D., T. F. Thornton, Jr., M.D., E. H. Storer, M.D., and James Clarke, M.D.

stimulant. The accumulation in the stomach of considerable amounts of such relatively pure fundic secretion obviously provides in man the counterpart of those experiments in animals where ulcers inevitably develop and become progressive.

The medical management of duodenal ulcer has been successful directly dependent upon the degree to which the acid gastric juice has been neutralized during the entire 24 hours. Surgical treatment, likewise, has been successful when a sufficient part of the fundus mucosa has been removed to reduce the

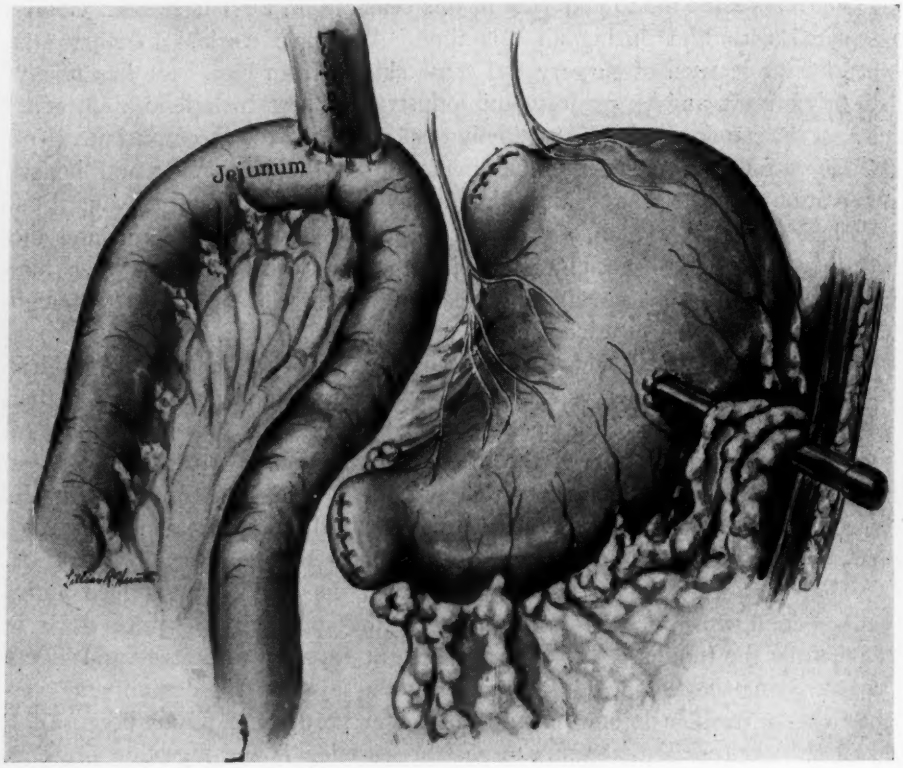


FIG. 1.—Diagram illustrating the totally isolated stomach preparation with preservation of the vagus innervation and blood supply.

gastric secretion to normal or subnormal values. The importance of the vagus nerves in the normal mechanism of gastric secretion has been recognized since the classical researches of Pavlov, and his pupils. However, it is possible that the discovery of humoral factors also effecting gastric secretion, notably gastrin and histamine, has directed the attention of many students to this phase of gastric physiology and has led to the employment of humoral stimuli exclusively in testing gastric secretory function in health and disease. Reliable data on the total volume of gastric juice secreted by normal man in 24 hours are very meager. There seems to be no way to apply the usual normal stimuli to the gastric glands and still recover the secretory product.

There is also little or no information concerning the relative proportion of gastric juice that is elicited by neurogenic stimuli and by humoral factors.

Some data bearing on this problem have been recently obtained in our laboratory, the details of which will be reported elsewhere. In this work, total isolated stomach pouches were prepared in dogs by the method of Dragstedt and Ellis.[3] The lower end of the esophagus was mobilized and the vagus nerves carefully pushed aside. The esophagus was then transected and the upper end of the stomach infolded and closed. The pylorus was then

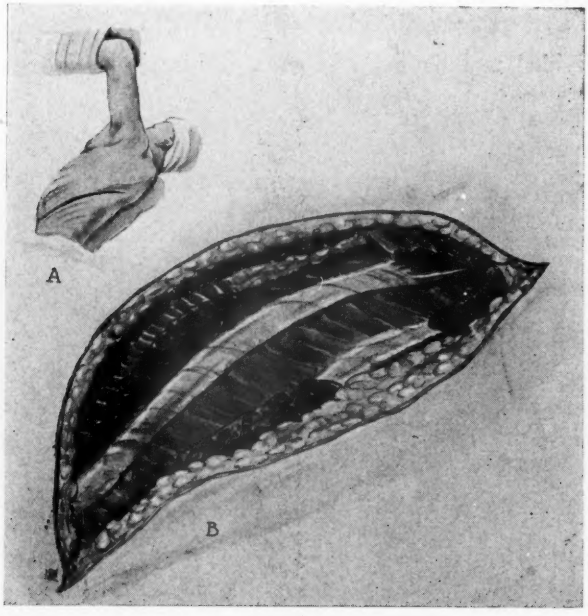


FIG. 2.—Incision (A) and exposure (B) of the 7th rib for transthoracic vagotomy.

transected, both ends infolded and closed, and the jejunum brought up and anastomosed to the esophagus by end-to-side suture. A gold plated cannula was inserted into the isolated stomach for the collection of gastric juice (Fig. 1). In a typical experiment such an isolated stomach, in which the blood supply and the vagus innervation had been carefully preserved, was found to secrete an average of 1,100 cc. of gastric juice with a free hydrochloric acid concentration of 0.35 to 0.42 per cent in 24 hours. The total secretion for a month was collected and then the vagus nerves were divided in the chest just above the diaphragm. The volume of gastric juice immediately declined to an average of 410 cc. with a free acidity of 0.11 to 0.32 per cent, and this effect persisted for at least 60 days.

By this type of experiment it was found that section of the vagus nerves to the stomach reduced the secretion of gastric juice in dogs to a half or even a fourth of the normal level. Unless it should develop that psychic factors are more important in gastric secretion in dogs than in man, it appears highly

probable that a similar reduction can be expected. The data obtained so far, suggest that the hypersecretion of gastric juice in ulcer patients is neurogenic in origin and that, consequently, a comparatively greater reduction should follow vagus section in man than in lower animals.

At the present time, 39 patients have been treated by vagus section in this Clinic. In 32 of these, the vagi have been divided in the left chest just above the diaphragm. The technic of this operation is illustrated in Figures 2, 3, and 4. An extensive resection of the seventh or eighth rib together with a portion of the cartilage is made so that retraction of the wound will produce minimum trauma. The intercostal nerve is isolated at the posterior margin of the wound, divided and ligated with silk. This procedure minimizes post-

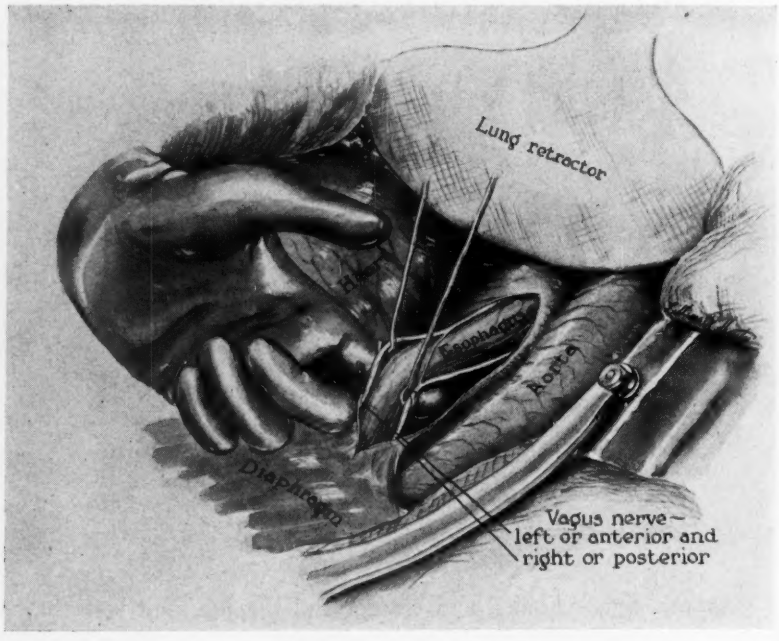


FIG. 3.—Mobilization of the esophagus and isolation of vagus nerves showing the communication between the anterior and posterior trunks.

operative pain in the chest, otherwise a troublesome complication. The inferior pulmonary ligament is clamped, cut, and ligated and the incision in the parietal pleura carried backward toward the aorta about 2 cm. The finger is then introduced through this aperture and the esophagus mobilized into the left chest by gentle blunt dissection. The vagus nerves may be easily identified by palpation, ligated with silk and divided as in Figure 3. The proximal ends of the divided nerves are sutured into the left pleural cavity to hinder regeneration. The chest is closed without drainage.

In seven of the patients, the vagus nerves have been divided below the diaphragm, usually because an associated high grade pyloric stenosis necessitated a gastro-enterostomy or resection to relieve obstruction. The method

employed is illustrated in Figures 5, 6 and 7. An inverted T-shaped incision (Fig. 5A) provides good access to the lower esophagus. The left triangular ligament of the liver is incised and the left lobe of the liver retracted medially (Figs. 5B and C). The peritoneal fold over the esophagus is severed and the esophagus mobilized by blunt dissection and pulled downward into the abdomen. Often 5 cm. or more of esophagus may be delivered into the abdomen by this method. The left, or anterior vagus nerve is found along the lesser curvature usually in the form of several separate strands which

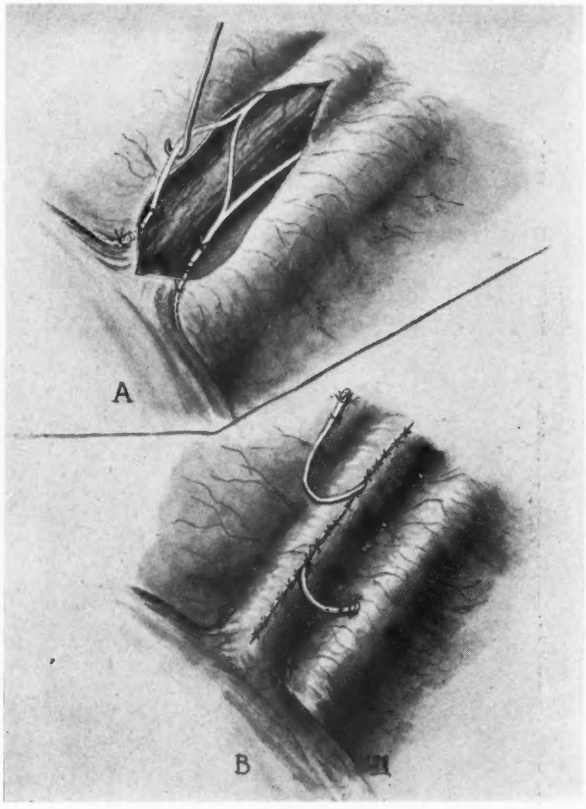


FIG. 4.—(A) Ligature and division of vagus nerves just above diaphragm; and (B) transplantation of proximal ends of cut vagi into the pleural cavity.

can be grouped together. The right, or posterior vagus is found along the greater curvature. It is most important to clear the esophagus of all nerve fibers for a distance of 2 or 3 cm. and to divide all the fibers passing to the stomach through the diaphragm. It is somewhat more difficult to secure a complete vagotomy by this abdominal approach but it can be accomplished if sufficient care is exercised. The nerve trunks are cut between silk ligatures and the proximal ends permitted to retract into the mediastinum, or they may be sutured to the diaphragm as in Figure 7.

The insulin test, as suggested by Hollander,[4] has been employed in our

TABLE I

TABULATED SUMMARY OF DATA ON PATIENTS UPON WHOM SECTION OF THE VAGUS NERVES WAS PERFORMED FOR GASTRODUODENAL ULCER

Patient	Unit No.	Age and Sex	Duration of Symptoms Years	Diagnosis	Direct Visualization of Ulcer with Gastroscope	Roentgen-ray Evidence of Ulcer Crater	Pyloric Stenosis	Hemorrhage	Perforation	Volume Preop. Night Secretion	Volume Postop. Night Secretion	Preop. Free Acid	Postop. Free Acid	Date of Vagus-Section	Remarks
H. F.	344351	54 ♂	20	Duodenal ulcer	−	+	+++	++	+	1142	395	44	35	10–25–44	Subdiaphragmatic vagotomy plus gastro-enterostomy. Complete relief. No recurrence to 5–10–1945
H. W.	329519	55 ♂	20	Duodenal ulcer	−	+	+++	++	−	1241	902	32	0	11–10–44	Subdiaphragmatic vagotomy plus gastro-enterostomy. Complete relief. No recurrence to June, 1945
C. B.	345581	42 ♂	26	Gastro-enterostomy 1928 Gastrocolic fistula 1930 Partial gastrectomy 1938 Gastrojejunal ulcer	−	+	−	+	+	200	177	13	0	11–18–44	Supradiaphragmatic vagotomy. Slight relief. Total gastrectomy July, 1945
M. B.	285298	56 ♂	12	Gastro-enterostomy 1942 Gastrojejunal ulcer	−	+	−	++	−	1021	412	22	36	11–24–44	Gastro - enterostomy taken down. Supradiaphragmatic vagotomy. Complete relief. No recurrence to June, 1945
J. W.	293108	60 ♂	25	Gastro-enterostomy 1936 Gastrojejunal ulcer	+	+	−	−	−	1220	338	20	0	11–27–44	Supradiaphragmatic vagotomy. Pain in incision, ulcer pain relieved. No recurrence to July, 1945
A. W.	346494	47 ♂	15	Gastro-enterostomy 1942 Gastrojejunal ulcer	−	+	−	++	0	566	361	0	0	12–11–44	Supradiaphragmatic vagotomy. Complete relief, with no recurrence to Feb. 1945
H. K.	345881	38 ♂	20	Duodenal ulcer	−	+	+	−	−	723	65	39	24	12–27–44	Supradiaphragmatic vagotomy. Complete relief. No recurrence to 5–6–45
H. M.	325181	30 ♂	7	Duodenal ulcer	−	+	+	+	−	775	428	36	6	12–29–44	Supradiaphragmatic vagotomy. Complete relief. No recurrence to May, 1945
N. K.	330562	48 ♂	7	Duodenal ulcer	−	+	+	+	−	717	400	55	19	1–3–45	Supradiaphragmatic vagotomy. Complete relief. No recurrence to April, 1945
M. C.	57621	54 ♂	20	Duodenal ulcer	−	+	−	−	−					1–5–45	Supradiaphragmatic vagotomy. Death from pneumonia

M. C.	57621	54 ♂	20	Duodenal ulcer	−	±	−	±	−					1–5–45	Supradiaphragmatic vagotomy. Death from pneumonia
E. T.	347888	60 ♀	15	Duodenal ulcer	−	+	++	−	−	786	358	44	0	1–8–45	Supradiaphragmatic vagotomy. Complete relief. No recurrence to July 1945
R. V.	343287	42 ♂	1	Duodenal ulcer	−	−	+	−	−	1043	486	82	61	1–10–45	Supradiaphragmatic vagotomy. Complete relief. No recurrence to April, 1945.
W.H.S.	345905	52 ♂	26	Duodenal ulcer	−	+	++++	−	−	1165	893	35	25	1–19–45	Subdiaphragmatic vagotomy plus gastro-enterostomy. Complete relief. No recurrence to April, 1945
J. P.	349287	54 ♂	8	Duodenal ulcer	−	−	+++	−	−	405	571	23	14	1–19–45	Subdiaphragmatic vagotomy plus gastro-enterostomy. Complete relief. No recurrence to April, 1945
W. W.	351791	57 ♂	2	Duodenal ulcer	−	−	++	−	++	756	523	54	15	2–23–45	Supradiaphragmatic vagotomy. Complete relief. No recurrence to July, 1945
G. P.	328604	48 ♂	20	Subtotal gastrectomy 4–3–44. Gastrojejunal ulcer	−	+	−	−	−	1126	233	12	0	3–12–45	Supradiaphragmatic vagotomy. Complete relief. No recurrence to July, 1945
M. S.	204878	42 ♂	6	Subtotal gastrectomy 1943. Gastrojejunal ulcer	−	+	−	+	−	310	395	6	0	3–23–45	Supradiaphragmatic vagotomy. Complete relief. No recurrence to June, 1945
G. K.	76605	43 ♂	4	Gastric ulcer	+	+	−	−	−	460	248	31	14	3–21–45	Supradiaphragmatic vagotomy. Roentgen-rays show marked decrease in ulcer crater in 6 weeks
W. K.	355373	52 ♂	15	Duodenal ulcer	−	+	+	−	−	1086	295	46	11	4–13–45	Supradiaphragmatic vagotomy. Complete relief. No recurrence to July 1945,
C. W. O.	4977	42 ♂	16	Duodenal ulcer	−	−	+			642	212	66	2	4–18–45	Supradiaphragmatic vagotomy. Complete relief. No recurrence to July, 1945
J. A.	333605	44 ♂	15	Duodenal ulcer	−	+	+++	−	−	627	347	35	0	5–20–45	Subtotal gastrectomy, plus subdiaphragmatic vagotomy. Complete relief. No recurrence to August, 1945
G. H.	270528	47 ♂	15	Duodenal ulcer	−	+	++			1838	630	19	0	6–20–45	Subdiaphragmatic vagotomy plus gastro-enterostomy. Complete relief. No recurrence to August, 1945
J. G.	359155	31 ♀	15	Duodenal ulcer	−	+	+	−	−	881	238	43	17	7–2–45	Subdiaphragmatic vagotomy.
T. M.	358801			Duodenal ulcer	−	+	−	++	−	1138	494	78	25	7–23–45	Supradiaphragmatic vagotomy.

work to determine if all the vagus secretory fibers to the stomach have been interrupted. This test depends upon the fact that the hypoglycemia induced by an adequate dose of insulin stimulates the vagus secretory fibers to the stomach probably by an effect on the central nervous system. As a rule, the injection of 20 units of insulin in a normal adult produces a fall in the blood

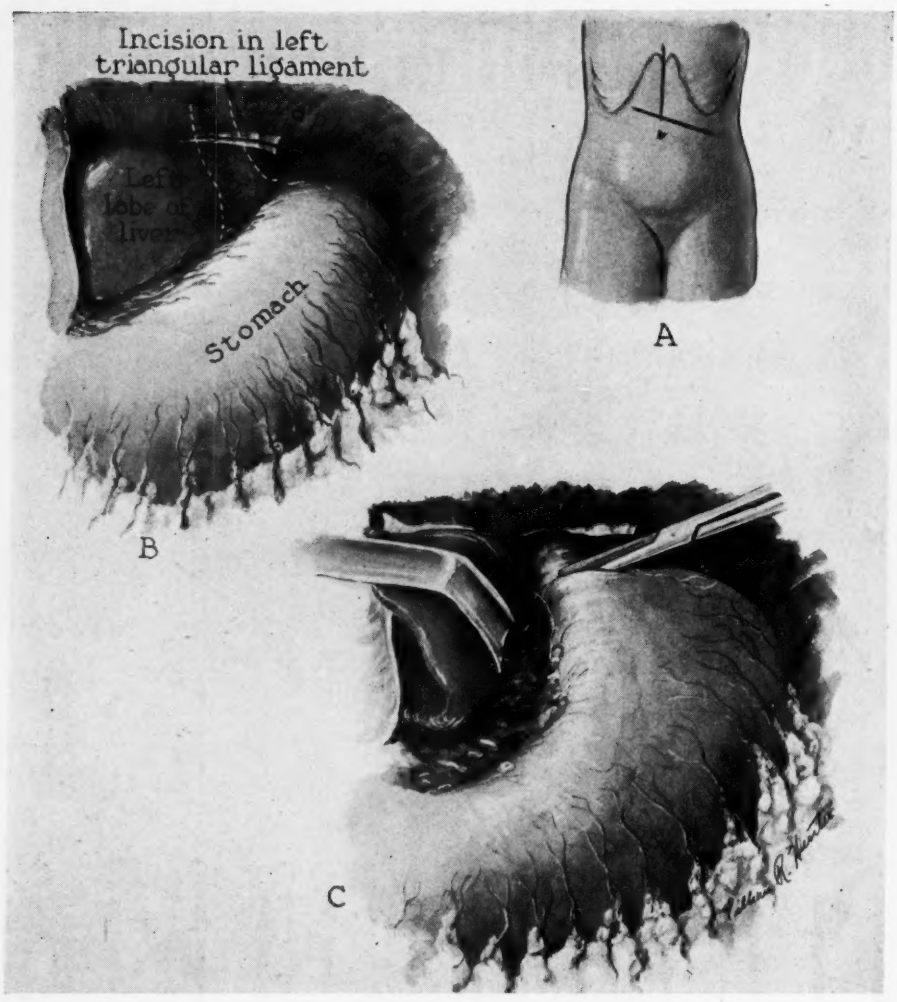


FIG. 5.—(A) Incision for transabdominal vagotomy. (B) Division of the left triangular ligament to the liver. (C) Exposure of esophagus.

sugar to 40 mg. or lower, and in about 30 minutes to an hour a marked augmentation in the rate and acidity of the fasting secretion results. No effect whatever occurs if the vagus section has been complete. The test must be controlled by estimations of the blood sugar before and one hour after the injection of insulin. The sugar must fall to 50 mg. or lower or no stimulation of the vagi is produced. In the last 21 patients, a positive response to the injection of insulin was obtained in 19 before operation, and this was

completely absent after the vagus section, except in one case where a doubtful positive response occurred in one test.

The data concerning the first 15 patients subjected to vagus section have been summarized in a previous report.[1] A tabulated summary of the remaining 24 is included here, Table I. Brief protocols of relevant data in the histories of these patients are also presented.

FIG. 6.—(A and B) Mobilization of esophagus.

It will be noted that one of the 39 patients died, a mortality for the operation at present of 2.5 per cent. This patient developed a postoperative bronchopneumonia due, in part to the aspiration of regurgitated material which had accumulated in the stomach. It is now our practice to maintain constant intragastric suction for three to four days after operation or until

the stomach has recovered sufficient tonus to prevent the accumulation of more than 200 cc. of fluid. There have been no other serious postoperative complications. As noted before, pain along the rib margin was a troublesome development in many of the early cases. This has been very largely prevented by the division of the intercostal nerve at the posterior margin of

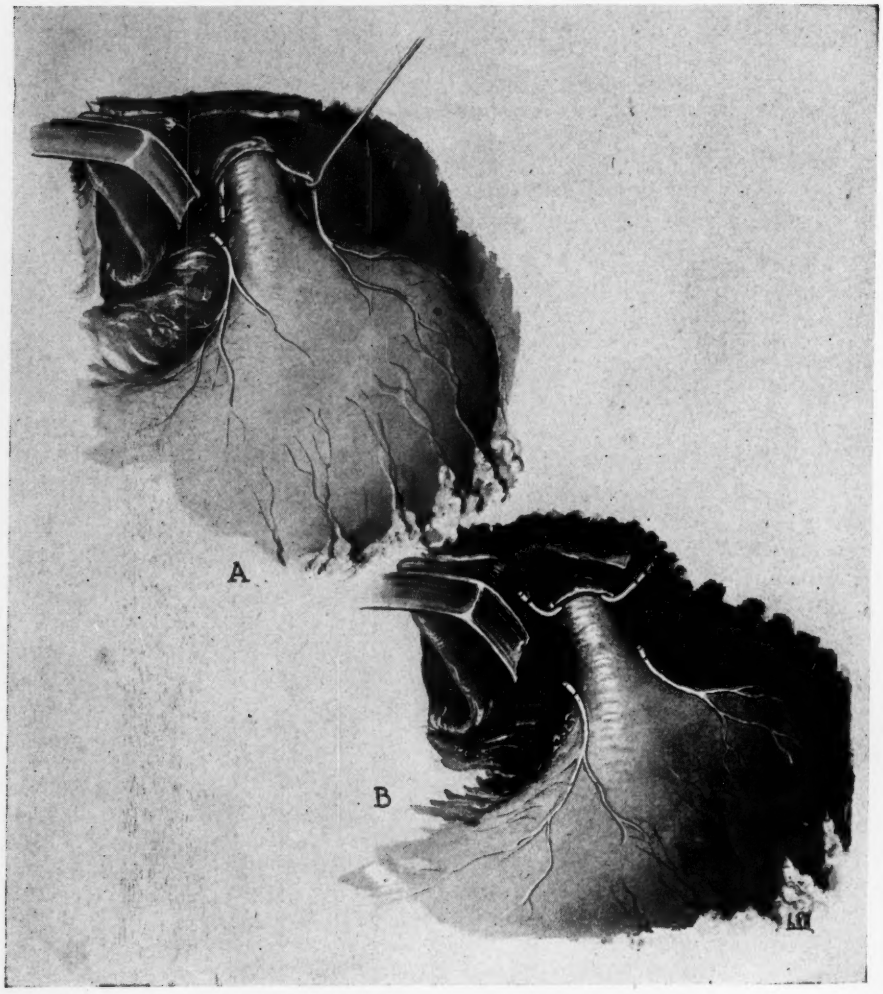


FIG. 7.—Isolation and division of vagus trunks.

the wound. It is probable that a pleural effusion of varying amount occurs in all patients, but this has required aspiration in only 25 per cent. A second aspiration was performed three times. There is undoubtedly a hazard from atelectasis and bronchopneumonia. The practice of early rising has probably lessened the incidence of these complications. Almost all of the patients get out of bed after 24 hours and remain so for long periods on the third or fourth day.[5]

Thirty of the patients subjected to vagus section had duodenal ulcers, two had gastric ulcers and seven had gastrojejunal ulcers. Eight of the duodenal ulcer patients were given a gastro-enterostomy in addition to the vagus section because of high grade pyloric stenosis. In five of these the vagus section was done by the abdominal approach at the same time as the gastro-enterostomy. Only one of the duodenal ulcer patients failed to obtain striking and persistent relief of symptoms, and in this case there were many features suggesting a neurosis. The first patients have been followed for two and one-half years and, so far, have remained well on unrestricted diets and without medication. One of the patients with gastric ulcer has been entirely cured of his disease as determined by gastroscopic and roentgenographic evidence and complete relief of symptoms. The other has been relieved of distress, and at the last examination a marked reduction in the size of the ulcer crater was apparent. The status of vagus section for gastrojejunal ulcers is more uncertain. These ulcers are notoriously difficult to heal without resection. Of the seven patients with this lesion, one was dissatisfied with the result and went to another clinic where a total gastrectomy was performed. One patient secured complete relief of distress only with additional alkalies, but was able to return to work as a sailor and has not been seen during the past year. The remaining five have secured complete relief of ulcer distress, and in three of these, a spectacular recession in the craters, visualized roentgenographically, has been obtained. A longer period of observation is required before conclusions can be drawn in this group.

Studies on the effect of vagus section on gastric secretion and motility in ulcer patients have been made, and will be reported in detail elsewhere. The operation has no effect on the secretory response of the stomach to histamine or caffeine but abolishes the stimulating effect of insulin hypoglycemia and a sham meal. Confirming our earlier experience, the most definite and consistent secretory abnormality in ulcer patients is an abnormally large continuous secretion of gastric juice in the empty stomach at night when there is no apparent stimulus. This occurred without exception. Vagotomy reduced this secretion from 50 to 60 per cent, indicating that it is largely neurogenic in origin. The tonus and hunger contractions of the stomach in patients with duodenal ulcer are usually excessive and are reduced but not abolished by vagotomy. A temporary atony of the fundic region was observed in two patients by fluoroscopy. It is very likely that this reduction in hypertonicity in part accounts for the immediate symptomatic relief so commonly produced. Although a decrease in the motility of the stomach was found in each case when the examination was made, no evidence has been obtained, so far, indicating a similar decrease in the motility of the intestines. If any effect at all has been produced, it is in the direction of increased peristalsis. A considerable proportion of the patients who complained of constipation before the operation have been even more gratified by the disappearance of this disturbance than by the relief of the ulcer distress. Further study of this effect is necessary.

CLINICAL PROTOCOLS

H. F. (Unit No. 344351), a 54-year-old white male, was first seen in this clinic on October 18, 1944. He gave a history of epigastric distress for the previous 20 years, during which time he secured partial relief by food and alkalies. Eight years ago he had an attack of nausea and vomiting and a profuse gastric hemorrhage. Shortly after this attack he was operated upon for a perforated duodenal ulcer. After recovery from the operation he followed an ulcer management with frequent feeding and powders faithfully. When he came to this clinic his abdominal pain had become more severe, vomiting was frequent and he had passed tarry stools for the preceding two days. Roentgenologic examination revealed a duodenal ulcer with a crater and high grade pyloric obstruction. On October 25, 1944, a celiotomy was performed and a stenosing duodenal ulcer demonstrated. The lower esophagus was mobilized, the vagus nerves ligated and divided, and a posterior gastro-enterostomy made. Recovery from the operation was uneventful, and the patient has had no epigastric distress of any kind subsequently. When last seen in May, 1945, he was eating a regular diet, without medication, and had no distress.

C. B. (Unit No. 345581), a 42-year-old white male, was first admitted to the clinic on November 7, 1944. He complained of epigastric distress occurring several hours after meals and at night ever since he was 16 years old. The ingestion of food or milk always relieved the pain. In 1928, a posterior gastro-enterostomy was done for duodenal ulcer. Following this operation his abdominal pain persisted and he developed diarrhea. He was operated upon again in 1930, at which time a gastrojejunocolic fistula was found. This was closed and the gastro-enterostomy taken down. The epigastric pain persisted and, in 1938, a subtotal gastrectomy was performed. This provided temporary relief, but early in 1944 symptoms recurred, and roentgenologic examination revealed a gastrojejunal ulcer. Medical management provided only partial and temporary relief and he began to vomit. Roentgenologic examination in this clinic on November 14, 1944, revealed a large jejunal ulcer. On November 18, 1944, a transthoracic supradiaphragmatic section of the vagus nerves was performed. Recovery was uneventful. On February 28, 1945, roentgenologic examination revealed a decrease in the size of the ulcer crater. The epigastric distress improved and he began to eat very well, but was severely injured in an automobile accident in 1945. He recovered from this accident but his epigastric distress recurred and he entered another clinic where a total gastrectomy was performed.

H. W. (Unit No. 329517), a 55-year-old white male, was first seen in this clinic on March 14, 1944. For the preceding 20 years he had been having epigastric pain after meals and at night. No adequate therapy was given during this period. On two occasions in 1943 he had massive gastro-intestinal hemorrhages. On June 24, 1944, roentgenologic examination revealed a duodenal ulcer with deformity of the duodenal bulb, stenosis and a crater. Medical management gave only partial relief. On November 10, 1944, a posterior gastro-enterostomy and a subdiaphragmatic section of the vagus nerves was performed. For several weeks after operation, the anastomosis functioned poorly. However, after two months he was able to eat regularly without distress, and by June, 1945, he gained 30 pounds in weight. At this time he was eating a regular diet, without powders, and had no epigastric pain.

M. B. (Unit No. 285298), a 56-year-old white male, was first seen in this clinic on June 20, 1942. Twelve years before he began to have epigastric distress, consulted a physician who made a diagnosis of duodenal ulcer. He was placed on medical management and did fairly well until ten days before entering the hospital, when he developed severe epigastric pain and had a massive hemorrhage. Subsequently, roentgenologic studies showed a duodenal ulcer with a large crater. Roentgenotherapy to the stomach was given and considerable improvement resulted. In November, 1942, he developed obstructive symptoms and a posterior gastro-enterostomy was performed. He was well

for one year following this operation but then symptoms recurred, and roentgenologic examination revealed a gastrojejunal ulcer. Medical management failed to give relief.

On November 8, 1944, the gastro-enterostomy was taken down and on November 24, 1944, a transthoracic supradiaphragmatic section of the vagus nerves was performed. Recovery from both operations was uneventful and when last seen in June, 1945, he was entirely symptom-free and eating a regular diet without alkalies.

J. W. (Unit No. 293108), a 60-year-old male, was first seen in the clinic on September 15, 1942. He gave a history of epigastric distress for the previous 25 years. In 1936, a gastro-enterostomy was performed. Epigastric distress recurred in 1940, and roentgenologic examination revealed a gastro-enterostomy and just above it, a large gastric ulcer. The ulcer was visualized with the gastroscope. Roentgenotherapy to the stomach was given and, on December 22, 1942, the ulcer disappeared, was not demonstrated on either roentgenographically or on gastroscopic examination. In August, 1943, symptoms recurred and the ulcer reappeared on the roentgenogram and on gastroscopy. Strict management was instituted with some decrease in the size of the ulcer but this increased again in the latter part of 1944.

On November 27, 1944, a transthoracic supradiaphragmatic section of the vagus nerves was performed. Recovery was uneventful but was complicated by persistent pain in the region of the incision, which has continued to the present. Roentgenologic examination, March 24, 1945, revealed a poorly functioning gastro-enterostomy with a stomal ulcer.

When last seen in June, 1945, the patient was eating fairly well, had little or no epigastric distress but still complained of pain in the chest.

A. W. (Unit No. 346494), a 47-year-old white male, was first admitted to the clinic on November 21, 1944. He complained of epigastric distress which had been present for the previous 15 years, and a diagnosis of a duodenal ulcer had been made. Diet and powders controlled the pain fairly well during this period. Symptoms recurred, however, and two years before entering the hospital, a gastro-enterostomy was performed elsewhere. Following this operation he was well until four hours before admission when he developed pain in his left side and began to vomit blood. The gastric hemorrhage was controlled and, on November 29, 1944, roentgenologic examination revealed a well-functioning gastro-enterostomy with a gastrojejunal ulcer with a crater. On December 11, 1944, a transthoracic supradiaphragmatic section of the vagus nerves was performed. Recovery from the operation was uneventful except for a slight pleural effusion on the left side which did not require tapping. Ulcer symptoms were entirely relieved and roentgenologic examination, January 9, 1945, failed to reveal the crater at the anastomosis. When last seen in February, 1945, he was free from distress, eating a regular diet, and taking no powders.

H. K. (Unit No. 345881), a 38-year-old white male, was admitted to the clinic on November 11, 1944. For the preceding 20 years he had been having intermittent gastric distress following meals. This was partly relieved by food and alkalies. Roentgenologic examination, November 15, 1944, revealed a duodenal ulcer with deformity and a small central crater. Medical management produced little or no effect. On December 27, 1944, a transthoracic supradiaphragmatic vagus section was performed. Recovery was uneventful. Roentgenologic examination, January 11, 1945, showed no change in the ulcer crater. On February 5, 1945, the crater appeared somewhat smaller and by May 10, 1945, it had completely disappeared on roentgenologic examination.

When last seen on May 6, 1945, he was eating a liberal diet, without powders, and without distress.

H. M. (Unit No. 325181), a 30-year-old white male, was first admitted to the hospital on January 12, 1944. Seven years previously he had epigastric pain occurring after meals. Roentgenologic examination was made, with a diagnosis of duodenal ulcer. Medical management produced marked relief but at intervals the epigastric distress recurred. Two months ago, he began to vomit and the abdominal pain became more

severe. On one occasion he had a severe hemorrhage. Roentgenologic examination revealed a duodenal ulcer, with deformity and a large ulcer crater. Roentgenotherapy to the stomach was given and the crater decreased somewhat in size but did not disappear. He did fairly well on medical management but on July 27, 1944, was readmitted to the hospital because of a massive hemorrhage. This was controlled and, December 29, 1944, a transthoracic supradiaphragmatic section of the vagus nerves was performed. Recovery was complicated by pleural effusion which required aspiration. Roentgenologic examination, April 11, 1945, revealed disappearance of the ulcer crater and no obstruction, but a persistent deformity of the duodenal bulb.

When last seen on May 15 he had no epigastric distress, was eating a regular diet and had gained 30 pounds since the operation.

N. K. (Unit No. 330562), a 48-year-old white male, was admitted to the clinics on March 28, 1944. For the preceding seven years he had been having intermittent epigastric pain coming on several hours after meals and relieved by food and alkalies. He passed black tarry stools at intervals but did not vomit blood. In 1942, he was operated upon elsewhere for ulcers of the stomach but the nature of the operation was not determined. The epigastric distress persisted and roentgenologic examination in this clinic, March 30, 1944, revealed a marked ulcer deformity of the duodenal bulb with a central crater. In April, 1944, he was given roentgenotherapy to the stomach and medical management. The symptoms were relieved and the crater disappeared. In December, 1944, the epigastric pain recurred, roentgenologic examination showed marked deformity but no crater. On January 3, 1945, a transthoracic supradiaphragmatic section of the vagus nerves was performed. Recovery was complicated by pain in the chest and from gastric distention. When last seen on April 5, 1945, he was eating a regular diet, without powders, and had no epigastric distress. He had gained 20 pounds since the operation.

M. C. (Unit No. 57621), a 54-year-old white male, was first seen in this clinic in 1932. He gave a history of epigastric distress of the ulcer type for the previous 20 years. Roentgenologic examination revealed deformity of the duodenal bulb with marked pyloric stenosis. A posterior gastro-enterostomy was performed. In June, 1934, his ulcer pain recurred, and roentgenologic studies revealed a gastrojejunal ulcer. Medical management gave only partial relief and, in December, 1934, the gastro-enterostomy was taken down. Within a few months his ulcer symptoms appeared again and persisted in spite of rigorous medical management combined with roentgenotherapy to the stomach to decrease gastric secretion. On January 5, 1945, a transthoracic supradiaphragmatic section of the vagus nerves was done. Following operation, he developed gastric distention, and on one occasion aspirated a considerable amount of vomitus. A bronchopneumonia developed and death occurred on January 13, 1945. Autopsy was not permitted.

E. T. (Unit No. 347888), a 60-year-old white female, was first seen in this clinic on December 13, 1944. She complained of epigastric pain after meals for the previous 15 years. One year ago, a roentgenologic examination was made, with a diagnosis of duodenal ulcer. Symptoms were relieved by medical management, but in July, 1944, she began to vomit. Roentgenologic examination on December 13, 1944, revealed partial pyloric obstruction due to a duodenal ulcer, with a crater. On January 8, 1945, a transthoracic supradiaphragmatic section of the vagus nerves was performed. Recovery was complicated by fever which persisted for a week, and a pleural effusion. Following operation, she was able to eat a soft diet without vomiting. No medication was given. Roentgenologic examination on January 30, 1945, showed some improvement in the pyloric obstruction but persistence of an ulcer crater in the duodenum. On May 8, 1945, the pyloric obstruction was markedly improved although the stomach was still somewhat dilated. When last seen on May 12, 1945, she was eating a liberal diet, without medication, and without epigastric distress or vomiting. Her only complaints were occasional sharp jabbing pain in the region of the incision.

R. V. (Unit No. 343287), a 42-year-old white male, was first admitted to the clinic on October 5, 1944. He gave a history of intermittent epigastric distress of the ulcer type for the previous eight months. For the past four months the pain had been particularly severe. Roentgenologic examination revealed a deformity of the duodenal bulb but no crater. Medical management failed to relieve the distress. On January 10, 1945, a transthoracic supradiaphragmatic section of the vagus nerves was performed. Recovery from the operation was uneventful, and all epigastric symptoms were immediately relieved. When last seen, March 31, 1945, he was feeling well, eating a liberal diet without distress or medication.

W. H. S. (Unit No. 345905), a 52-year-old white male, was first seen in the clinic on November 13, 1944. For the preceding 26 years he had been having periodic attacks of severe epigastric pain relieved by food and alkalies. In 1929, these attacks began to be associated with vomiting. Roentgenograms revealed a duodenal ulcer. On medical management he remained fairly well until 1938, when the epigastric pain and vomiting became more severe. These symptoms continued and were associated with a loss of 20 pounds in weight during the five months before admission to the clinics. Roentgenologic examination at this time revealed almost complete pyloric obstruction. On January 19, 1945, a posterior gastro-enterostomy was performed, and at this time the vagus nerves were divided immediately beneath the diaphragm. Recovery from the operation was uneventful and during the first three months the patient gained 30 pounds in weight. When last seen March 27, 1945, he was eating a regular diet, without medication, and without epigastric distress.

J. P. (Unit No. 349287), a 54-year-old white female, was admitted to this clinic on January 10, 1945. She complained of intermittent epigastric pain that was relieved by food and alkalies for the preceding eight years. For the past two years this was associated with vomiting and a loss of 35 pounds in weight. Roentgenology examination, January 10, 1945, revealed marked pyloric obstruction probably due to duodenal ulcer but no crater was visualized. On January 19, 1945, a celiotomy was performed by Dr. William Adams which revealed a large duodenal ulcer with adhesions. The esophagus was mobilized and the vagus nerves isolated. A segment, approximately one inch in length was resected from each vagus nerve. An anterior gastro-enterostomy was then performed. Recovery from the operation was complicated by a severe blood transfusion reaction. When last seen, March 30, 1945, she was feeling well, had no epigastric distress and was eating a regular diet, without powders.

W. W. (Unit No. 351791), a 57-year-old white male, was first admitted to this clinic on February 16, 1945. He reported that he had been entirely well until November, 1943, when he developed a severe epigastric pain for which an emergency operation was performed. A perforated duodenal ulcer was found, and closed. He remained well until December, 1944, when he again had a perforated duodenal ulcer for which he was operated upon and which was again closed. He remained well then until February, 1945, when he developed an attack of severe upper abdominal pain with vomiting. Nine days after this attack he was admitted to the hospital for observation. Roentgenologic examination, February 19, 1945, revealed marked deformity of the duodenal bulb and pyloric stenosis of moderate degree. A crater was not demonstrated. On February 23, 1945, a supradiaphragmatic transthoracic section of both vagus nerves was performed. Recovery from the operation was uneventful. When last seen on July 24, 1945, he stated that he had been completely relieved of all ulcer symptoms since the operation. He was eating a liberal diet without distress or vomiting, and took no medication of any kind.

G. P. (Unit No. 328604), a 48-year-old white male, was admitted to the clinic on March 2, 1944. Twenty years before he first experienced abdominal pain accompanied by nausea and vomiting. A diagnosis of duodenal ulcer was made. Medical treatment proved unsuccessful and, in 1925, a gastro-enterostomy was performed. This gave only temporary relief and, in 1939, roentgenologic studies revealed a gastrojejunal ulcer. He

continued to have epigastric distress with occasional episodes of vomiting during the ensuing five years. When he entered the clinic, roentgenologic examination of the stomach, March 8, 1944, revealed a large gastrojejunal ulcer. On April 3, 1944, the gastro-enterostomy was taken down and a subtotal gastrectomy was performed. Symptoms were entirely relieved until February, 1945, when the abdominal pain returned. Roentgenologic examination, February 14, 1945, revealed the reappearance of a very large gastrojejunal ulcer. On March 12, 1945, a transthoracic supradiaphragmatic section of the vagus nerves was performed. Immediate relief followed this operation and he was able to eat a liberal diet, without medication. Subsequent roentgenologic studies, April 30, 1945, showed almost complete disappearance of the ulcer crater.

M. S. (Unit No. 204878), a 36-year-old male, was first seen on August 29, 1938. For the past two months he had been complaining of typical ulcer distress and roentgenologic examination revealed a duodenal ulcer, with a crater. Symptoms were controlled for a time on medical management but recurred in 1943, at which time a subtotal gastrectomy was performed. At operation, a chronic duodenal ulcer penetrating into the pancreas was found. Six months after the operation a recurrence of symptoms developed and a gastrojejunal ulcer was demonstrated roentgenologically. Roentgenotherapy to the stomach was then given, with relief of symptoms, and there was apparent disappearance of the ulcer. The ulcer recurred in six months and pain became severe. On March 23, 1945, a transthoracic supradiaphragmatic section of the vagus nerves was performed. Recovery was uneventful, and the patient was entirely relieved of ulcer distress. On May 9, 1945, roentgenologic examination failed to reveal any evidence of the gastrojejunal ulcer.

When last seen in June, 1945, he was symptom-free and ate a regular diet, without powders.

W. K. (Unit No. 355373), a 52-year-old white male, was first admitted to the clinic on April 9, 1945. He gave a history of typical ulcer distress for the preceding 15 years. Medical management had usually been successful in providing relief but frequent recurrences of pain and distress occurred. In the four months before entering the hospital the pain had been unusually severe and failed to respond to the usual therapy. Roentgenologic examination revealed a duodenal ulcer, with a large crater. On April 13, 1945, a transthoracic supradiaphragmatic section of the vagus nerves was performed. Recovery from the operation was uneventful and was followed by complete relief of his ulcer distress. When last heard from in July, 1945, he was eating a liberal diet, without medication, and experienced no abdominal pain or discomfort.

C. W. O. (Unit No. 4977), a 42-year-old white male, was admitted to the clinics on April 15, 1945. He gave a history of epigastric distress beginning in 1928, at which time roentgenologic examination revealed a duodenal ulcer. Medical management was faithfully carried out and this provided complete relief of all symptoms except during periods of severe mental strain. At this time, the pain recurred and interfered so much with his work as a trial lawyer that further treatment was desired. Roentgenologic examination revealed a deformity of the duodenal bulb but no crater. On April 18, 1945, a transthoracic supradiaphragmatic section of the vagus nerves was performed. Recovery from the operation was uneventful and following this, all of his ulcer symptoms have entirely disappeared. When last seen in July, 1945, he was eating a liberal diet, without medication, and had no ulcer symptoms.

CONCLUSIONS

1. Descriptions are given of methods for the division of the vagus nerve supply to the stomach in man by a transthoracic and an abdominal approach.
2. The vagus nerves to the stomach were divided in 30 patients with duodenal ulcers, in two with gastric ulcers, and in seven with gastrojejunal ulcers.

3. A striking and persistent relief of ulcer distress has been almost uniformly secured, with gain in weight, and roentgenographic evidence of healing of the lesions.
4. Section of the vagus nerves had no effect on the secretory response of the stomach to histamine or caffeine but abolished the response to insulin hypoglycemia and a sham meal.
5. The tonus and motility of the stomach were decreased but not abolished by the operation.

REFERENCES

[1] Dragstedt, L. R., and Owens, F. M., Jr.: Proc. Soc. Exper. Biol. and Med., **53**, 152, 1943. Dragstedt, L. R., Palmer, W. L., Schafer, P. W., and Hodges, P. C.: Gastro-enterology, **3**, 450, 1944. Dragstedt, L. R., and Schafer, P. W.: Surgery, **17**, 742, 1945.

[2] Dragstedt, L. R.: ANNALS OF SURGERY, **102**, 563, 1935; *idem:* Arch. Surg., 44, 438, 1942.

[3] Dragstedt, L. R., and Ellis, J. C.: Amer. Jour. Physiol., **93**, 407, 1930.

[4] Hollander, F.: Gastro-enterology, **3**, 463, 1944.

[5] Schafer, P. W., and Dragstedt, L. R.: Surg., Gynec. & Obst., **81**, 93, 1945.

BLOOD PRESSURE OF RENAL AND OF EARLY AND LATE NEUROGENIC HYPERTENSION DOGS AFTER LOW CERVICAL CORD SECTION*

KEITH S. GRIMSON, M.D.

DURHAM, N. C.

FROM THE DEPARTMENT OF SURGERY, DUKE UNIVERSITY SCHOOL OF MEDICINE, DURHAM, N. C.

ESSENTIAL DIFFERENCES between experimental neurogenic and experimental renal hypertension have been reviewed and correlated with clinical hypertension and surgical treatment by sympathectomy.[1] The neurogenic hypertension produced by excision of the carotid sinuses and denervation of the cardio-aortic pressure sensitive areas is effected by altering reflex vasomotor regulation. Elevation of the blood pressure may be prevented or eliminated by complete sympathectomy. The renal hypertension produced by constriction of the renal artery or by capsules about the kidney, is effected by an humoral process. Elevation of blood pressure by this mechanism occurs in the presence or in the absence of the paravertebral sympathetic chains. The angiotonen or hypertensin associated with this form of hypertension will constrict a sympathectomized vascular bed.

Evaluation of the relative importance of abnormal blood pressure regulation over the sympathetic nervous system, of abnormal vasoconstriction by renal metabolic products through the blood stream, or of abnormal peripheral resistance effected by vascular arteriolar disease in the patient with hypertension is difficult. The author has suggested that vasomotor instability may initiate hypertension in certain patients and later produce arteriolar disease and a renal humoral mechanism. Should vasomotor instability be an initiating and a perpetuating factor in the hypertensive disease process of a patient adequate sympathectomy might block the initial development or arrest or delay the late developments. Should arteriolar disease be an early factor sympathectomy could offer only minor or secondary benefit.

Reed, Sapirstein, Southard, and Ogden[2] have found that rats with early renal hypertension and rats with chronic renal hypertension respond differently to nembutal anesthesia and to yohimbine hydrochloride. They suggest that "the renal pressor mechanism which initiates experimental renal hypertension is later superseded by a neurogenic mechanism mediated through the sympathetic nervous system." If correct, this observation will be significant. Occasional patients that have had primary kidney disease and have recovered have remained hypertensive and have responded to sympathectomy.

The patient with hypertension often has neurogenic, renal, and arteriolar disease in varying degrees. Further studies related to possible overlaps between varieties of experimental hypertension seem indicated.

* Much of this experimental work was done at the University of Chicago under the direction of Dr. D. B. Phemister.

The experiments reported below were undertaken to determine whether an experimental neurogenic hypertension in the dog could effect the development of detectable renal humoral vasoconstriction. Low cervical cord sections were employed to differentiate humoral from reflex vasoconstriction.

The effect of destroying the cord and of pithing the brain of the normal and of the renal hypertensive rat has been reported by Dock and Rytand.[3] Similar studies with the rabbit were reported by Dock.[4] The blood pressure of the normal and of the renal hypertensive animals fell rapidly to low levels. The rabbits formerly hypertensive exhibited higher elevation of blood pressure after the injection of epinephrine than occurred in pithed normal rats.

Glenn, Child, and Page[5] investigated the effect of low cervical cord section and destruction of the distal segment of cord upon the blood pressure of dogs with hypertension produced by Goldblatt clamps applied to the renal arteries. An immediate drop of pressure occurred that was replaced within five to 25 days by a definite restoration of hypertension levels that approached those observed before destruction of the cord. Glenn and Lasker[6] destroyed the spinal cords below C_6 in normal dogs. Surgical shock with low or imperceptible blood pressure occurred during the first several hours. The blood pressure returned to normal values after two to seven days. Constriction of renal arteries then produced hypertension.

Cord section at C_7 has been employed in six normal dogs, five dogs with renal hypertension, four dogs with neurogenic hypertension of 122 to 176 days' duration, and three dogs with neurogenic hypertension of 15 to 22 months' duration. Chloralose 0.1 Gm./Kg. was administered intravenously before each experiment. Artificial respiration was given routinely through a tracheal cannula. Blood pressures were recorded directly from one femoral or one carotid artery through tubing connected with a recording mercury manometer. Citrate or heparin was used in the tubing fluid. One hundred to 300 cc. of saline was given intravenously during the laminectomy. Careful hemostasis was employed during the exposure of the lower cervical spinal cord to minimize shock. The blood pressure was recorded without disturbing the animal for 10 to 20 minutes after exposure. The spinal cord at C_7 was then quickly frozen with CO_2 and completely transected using sharp scissors. A sponge was placed in the defect. The skin edges were clipped together over the sponge. Further observations were made without disturbing the animal.

CERVICAL CORD SECTION IN NORMAL DOGS

The blood pressures of six normal dogs were determined by puncture of the femoral arteries. The pressures ranged from 112 to 142, and averaged 132. After chloralose anesthesia they were again determined by needle puncture. The blood pressures ranged from 132 to 148, and averaged 138. After cannulae were inserted into the trachea and the femoral artery and the cord were exposed the blood pressures ranged from 130 to 152, and averaged 144. The spinal cord was then frozen and severed at C_7. Twenty minutes

later the pressures ranged from 74 to 100, and averaged 89. Sixty minutes after cord section the pressures ranged from 50 to 80, and averaged 71. The pressures of five observed two hours ranged from 70 to 80, and averaged 77. Three observed longer than three hours had further lowering to 64, 68, and 70.

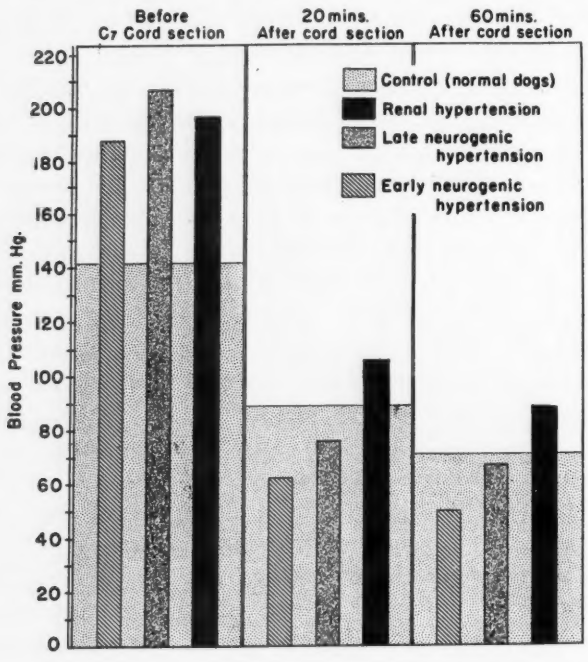


FIG. 1.—The average blood pressure of five dogs with renal hypertension, four dogs with early neurogenic hypertension, and three dogs with late neurogenic hypertension are compared with the average blood pressure of six normal dogs before and 20 minutes and 60 minutes after cord section. Elimination of central reflex vasopressor control reduces the blood pressure of dogs with neurogenic hypertension below control values and leaves the pressure of dogs with renal hypertension above control values.

CORD SECTION IN RENAL HYPERTENSION DOGS

Five dogs with renal hypertension produced by removing one kidney and applying tight linen capsules about the other were sacrificed in similar low cervical cord section experiments. Blood pressures by puncture of the femoral artery ranged from 202 to 216, and averaged 212. Blood pressures by artery puncture under anesthesia ranged from 196 to 228, and averaged 213. After preparation and just before freezing and division of the cord the pressures ranged from 180 to 215, and averaged 197. Twenty minutes after severing the cord the pressures ranged from 80 to 170, and averaged 116. Sixty minutes after cord section the pressures ranged from 50 to 138, and averaged 88. Two hours after section the pressures ranged from 40 to 146, and averaged 79. Saline solution was later given intravenously to four of the dogs in amounts varying from 150 to 300 cc. It effected elevation of the pressures from a range of 40 to 72, and an average of 61, to a range of 90

to 128, and an average of 114. This elevation persisted during the further period of observation of 0.5 to one hour. The fifth dog received no saline and had a pressure 2.5 hours after cord section of 140. The blood pressures of all dogs at the time of sacrifice 2.5 to three hours after low cervical cord section ranged from 90 to 140, and averaged 120.

CORD SECTION IN EARLY NEUROGENIC HYPERTENSION DOGS

Four dogs with neurogenic hypertension produced by excision of both carotid sinuses, division of one vagus-depressor-sympathetic trunk, and division of the other depressor-sympathetic trunk were sacrificed in similar low cervical cord section experiments. The hypertension had been present 122 to 176 days. Blood pressures by puncture of the femoral artery ranged from 200 to 256, and averaged 224. Pressures by artery puncture after anesthesia ranged from 174 to 260, and averaged 220. After preparation and just before freezing and transection of the low cervical spinal cord the pressures ranged from 164 to 200, and averaged 188. Twenty minutes after cord section the pressures ranged from 52 to 68, and averaged 62. Sixty minutes after section they ranged from 44 to 54, and averaged 50. A further decline of pressure was observed in dogs observed longer than one hour.

CORD SECTION IN LATE NEUROGENIC HYPERTENSION DOGS

Three dogs with neurogenic hypertension were observed 15, 21, and 22 months before being sacrificed in cord section experiments. The arterial blood pressures were 238, 234, and 230 before and 194, 242, and 230 after anesthesia. The pressures after preparation and before cord section were 210, 206, and 212. Twenty minutes after section they were 80, 70, and 78. Sixty minutes after section they were 86, 70, and 50. The pressure of one dog observed 2.25 hours fell from 86 at one hour to 70.

Discussion.—The blood pressure of normal dogs and of dogs with renal or neurogenic hypertension is little altered by chloralose anesthesia or by the operative preparation for cord section. Persistence of neurogenic hypertension during anesthesia, sedation, and natural sleep has been described.[7] Anesthetics or rest with sodium amytal, or other sedation, does not differentiate experimentally or clinically between reflex, humoral, or vascular disease components of hypertension.

The possible relationship between these elements in animals, or in patients, with hypertension is important. Elimination of all significant vasoconstrictor pathways by a total sympathectomy should block a reflex disturbance but should not correct renal or vascular disease. Low cervical cord section experiments have differentiated experimental renal from experimental neurogenic hypertension. The cords were frozen with CO_2 before section to reduce the immediate effect of stimulation of the cord by transection.

The effect of section of the low cervical spinal cord upon the blood pressure of normal dogs, renal hypertension dogs, and early and late neurogenic

hypertension dogs is illustrated in Figure 1. The dogs with renal hypertension exceed the blood pressure of the normal dogs before cord section and also 20 and 60 minutes after cord section. This is compatible with the presence in the blood stream of angiotonen, or hypertensin, acting peripherally independent of central vasoconstriction. Two hours after elimination of central vasomotor tone by cord section 150 to 300 cc. of saline elevated the average pressure of five renal hypertension dogs from 61 to 114. The higher pressure level persisted during the last half-hour to one hour of observation. This elevation is also compatible with the presence in the animal of an humoral vasoconstrictor capable of increasing blood pressure as the conditions of the circulation of the blood are improved.

Low cervical cord section in animals with early and late neurogenic hypertension produced a lowering of pressure below the levels observed in normal dogs. This lowering was most pronounced in animals with hypertension present 122 to 176 days. It was also significant in animals with hypertensions of 15, 21, and 22 months' duration. A moderate hypertension can be produced by renal vasoconstriction.[8] Renal denervation, however, does not alter experimental neurogenic hypertension.[9] The relative importance of a renal factor in experimental neurogenic hypertension has not been determined. The cord section experiments would indicate that loss of the abnormally increased reflex vasopressor influences to the entire body left them with less than normal intrinsic and humoral peripheral vascular tone. Humoral vasoconstrictors, if present, were not able to maintain blood pressures equivalent to those of normal dogs.

CONCLUSION

The evidence obtained by section of the cervical spinal cord at C_7 indicates that neurogenic hypertension early and after 15, 21, and 22 months does not develop a detectable humoral vasoconstrictor influence like that developed in renal hypertension by angiotonen or hypertensin.

BIBLIOGRAPHY

[1] Grimson, K. S.: The Surgical Treatment of Hypertension. Surg., Gynec. & Obst., **75**, 421–434, 1942.

[2] Reed, R. K., Sapirstein, L. A., Southard, F. D., and Ogden, Eric: The Effects of Nembutal and Yohimbine on Chronic Renal Hypertension in the Rat. Amer. J. Physiol., **141**, 707–712, 1944.

[3] Dock, W., and Rytand, D. A.: Absence of Vasoconstrictor Substance in Blood of Rats with Renal Hypertension. Proc. Soc. Exp. Biol. and Med., **32**, 374–375, 1934.

[4] Dock, W.: Vasoconstriction in Renal Hypertension Abolished by Pithing. Amer. J. Physiol., **130**, 1–8, 1940.

[5] Glenn, F., Child, C. G., and Page, I.: The Effect of Destruction of the Spinal Cord on Hypertension Artificially Produced in Dogs. Amer. J. Physiol., **122**, 506–510, 1938.

[6] Glenn, F., and Lasker, E. P.: The Effect of Destruction of the Spinal Cord on the Artificial Production of Hypertension in Dogs. Amer. J. Physiol., **124**, 106–109, 1938.

[7] Grimson, K. S., Kernodle, C. E., and Hill, H. C.: The Effect of Activity, Rest, Natural Sleep, Pentothal Sodium, Chloralose, and Ether on Experimental Neurogenic Hypertension and of Rest and Sodium Amytal and Anesthesia on Hypertensive Patients. J. A. M. A., **126,** 218–221, 1944.

[8] Grimson, K. S., Bouckaert, J. J., and Heymans, C.: Production of a Sustained Neurogenic Hypertension of Renal Origin. Proc. Soc. Exp. Biol. and Med., **42,** 225–226, 1939.

[9] Grimson, K. S.: The Sympathetic Nervous System in Neurogenic and Renal Hypertension. Arch. of Surg., **43,** 284–305, 1941.

CUTIS GRAFTS

CLINICAL AND EXPERIMENTAL STUDIES ON THEIR USE AS A REINFORCING PATCH IN THE REPAIR OF LARGE VENTRAL AND INCISIONAL HERNIAE

HENRY N. HARKINS, M.D., PH.D.
BALTIMORE, MD.

FROM THE DEPARTMENT OF SURGERY,
JOHNS HOPKINS UNIVERSITY MEDICAL SCHOOL AND HOSPITAL, BALTIMORE, MD.

SINCE LOEWE'S REPORT, in 1913, cutis grafts have been sporadically adopted for two purposes: (1) In the field of plastic surgery where the cutis is utilized to fill in tissue defects; and (2) in the operative treatment of hernia where patches of cutis are applied to strengthen the repair.

Cutis may be defined as the deeper layers of the skin which have been stripped of their epidermal covering. Anatomically, this includes approximately the deeper three-quarters of the thickness of the skin, the entire skin averaging about 1 mm., or 40/1000 inches, in depth. Histologically, cutis emprises the dermal layer with no epidermal covering, but with sebaceous and sudoriferous glands and occasional hair follicles as well as some of the underlying subdermal fat.

Reports in the literature on the use of cutis grafts, particularly as applied to the repair of hernia, include the following:

1. Loewe (1913) reported the use of cutis grafts in five cases of hernia and one of tendon repair. In describing the technic for removal of the graft, this author stated that the skin was removed with a scalpel in the manner of any full-thickness graft. The epidermis was then abraded away by scraping, as one would clean a carrot. The remaining tissue was then sutured over the defect under tension and the donor area was allowed to granulate and heal by second intention.

2. Rehn (1914) reported experiments on the use of cutis material. Strips of twisted cutis were used as insert grafts in the Achilles tendon of dogs. Rehn stated that under the influence of continual tension, a gradual degeneration of epithelial elements occurred, and that the tissue assumed the appearance and functions of normal tendon in about ten weeks.

3. Loewe (1929) extended his observations on the clinical use of cutis grafts to almost 100 cases.

4. Straatsma (1932) used buried cutis grafts for saddle-nose repair.

5. Uihlein (1939) reviewed the work of Rehn and presented 104 cases done in the latter's University Clinic in Freiburg since 1928. Eighty of these operations were for hernia.

6. Cannaday (1942) was the first writer to report the use of cutis grafts in hernial repair in this country, presenting 14 such cases. In 1943, this author made a later report, adding to his original cases and bringing the total to 37, 27 of which were operations for hernia.

7. Swenson (1943) reported two incisional herniae which were repaired with cutis graft reinforcement.

8. Scola (1944) reported the use of cutis grafts in the repair of two recurrent inguinal herniae and three incisional herniae. The cutis grafts were prepared by Scola's special method (*vide infra*) and in the operations on two of the incisional herniae formed the chief support, it being stated that "the fascia could not be closed."

9. Cannaday (1944) reported a total series of 107 operations utilizing cutis grafts, 56 of which were operations for hernia. Cannaday is at present the chief advocate of this technic in this country and expresses his position by stating: "Cutis may be used for any and every purpose for which fascia has been used, with the expectation of better results. . . . After this clinical experience with the uses of cutis (derma) in repair surgery, I am convinced that it is one of the most useful autoplastic repair materials that we have, that it is superior in strength to fascia lata and of much easier availability; that success in its use can be expected in a large percentage of cases; that it is of especial value in the surgical repair of large incisional herniae."

METHOD OF OBTAINING CUTIS

Cutis is obtained by removing a full-thickness skin graft and, in turn, separating the latter into its deep larger (cutis) and superficial layer (epidermis). The cutis is used for the hernial repair and the epidermis is either discarded (by some authors) or utilized to cover the donor area as a skin graft. These methods can be classified as follows:

1. *Original Loewe Method (1913):* A full-thickness graft is removed with a scalpel and then the epidermis is scraped off the graft with a razor. The donor site is allowed to granulate.

2. *Rehn Method (Uihlein, 1939):* A Thiersch graft is removed from the thigh and in the exposed bed a cutis graft of desired size is cut. The Thiersch graft is presumably resutured over the defect.

3. *Rehn's "Türflügel" Method (Uihlein, 1939):* The cutis is cut from a portion of abdominal wall to be discarded (as when doing a lipectomy in association with the repair of an incisional hernia). This obviates all necessity for closing the donor site. The method is only applicable to obese patients with incisional herniae, and has the objection that the neighboring skin is often atrophic and contains striae.

4. *Dermatome Flap Method of Swenson and Author (1943):* This technic is similar to the Rehn method (No. 2 above) except that the epidermis is cut off with a dermatome and one end is left attached. This saves time and allows for a neater closure of the donor wound.

5. *Method of Scola (1944):* A full-thickness dermatome flap (0.040 to 0.050 inch) is cut and one end left attached. Fresh glue is applied to the dermatome which then shaves the epidermis off the full-thickness flap at a depth of 0.008 inch, beginning at the attached end. The underlying cutis is then disattached for use and the free piece of epidermis sutured over the donor defect. This method has the advantage of cutting the cutis so that not only its superficial, but its deep surface is smooth and regular. This also represents the first

method where the cutting of the cutis is entirely mechanically controlled and where its thickness is known, at least within the limits of accuracy of the dermatome.

6. *Split-split Method:* In 1945, Zintel, of Philadelphia, reported the split-split method for increasing the yield of skin grafts from donor sites of limited size in extensive burns. The principle of the method is simply the splitting of a Padgett skin graft into two layers of equal thickness on the drum by resetting the blade. For adults the entire thickness was 0.020 to 0.028 inches and the two component halves were 0.010 to 0.014 inches. The idea presented itself to the author of utilizing Zintel's method for the preparation of cutis grafts. A thicker original setting (about 0.040 inches or more) is used and then the epidermis is cut off at a depth of about 0.010 to 0.020 inches and sutured on the donor area. The inner cutis layer is used for reinforcement of the hernia. The cutis so obtained is of known and regular thickness, but if the dermatome has a loose axle, tends to be too thin.

ANALYSIS OF CLINICAL CASES

Eleven patients, nine with ventral incisional herniae and two with epigastric herniae, were operated upon with silk closure of the fascia reinforced with an overlying patch of cutis. These operations were performed during the two-year period from May 13, 1943, to February 28, 1945. All operations except one (Case 4, done by Dr. George Duncan, Resident in Surgery at the Johns Hopkins Hospital) were performed by the author. Cases 1 and 2 were seen at the Henry Ford Hospital, and the remainder of the operations were performed at the Johns Hopkins Hospital.

Age: The patients varied in age from 36 to 56 years, with an average of 44 years.

Sex: Eight of the patients were females and three were males.

Weight: In ten cases where the weight was given all but one exceeded 205 pounds, with the heaviest patient (Case 4) weighing 263 pounds.

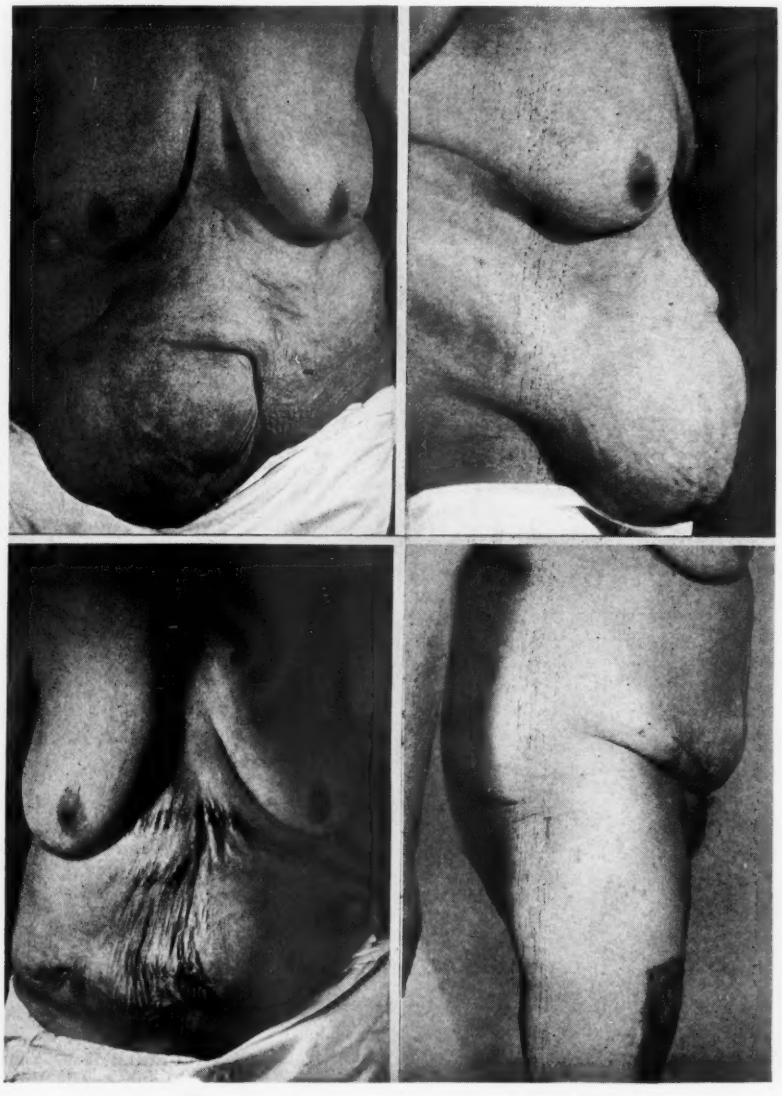
Previous Operation: Nine patients had previous operations as follows: Appendicectomy, with drainage—3 cases, cholecystectomy—2 cases, pelvic operations—3 cases, operation for "swallowed glass in intestines in 1919"—1 case. These operations had all been performed before 1941.

Duration of Hernia: The onset of the hernia varied from 1924 to 1943, with an average date of onset of 1936 (seven years before this series).

Previous Attempts at Repair: This had been done in five of the 11 cases, four of these operations being performed elsewhere. The exception (Case 2) deserves further explanation. On December 8, 1942, an hysterectomy and Mayo repair of a para-umbilical hernia was performed by the author. Six months later a swelling was diagnosed as a recurrence and operation was performed. Before starting the abdominal part of the operation, a strip of cutis was taken from the right thigh by the dermatome flap method. Afterwards, the abdominal operation revealed no recurrent hernia and only an aseptic serocele containing clear fluid. The wall of the serocele was excised and the cutis used

to reinforce the already strong previous repair. Two years later the patient presented no signs of recurrence and had no symptoms referrable to the operation.

A B



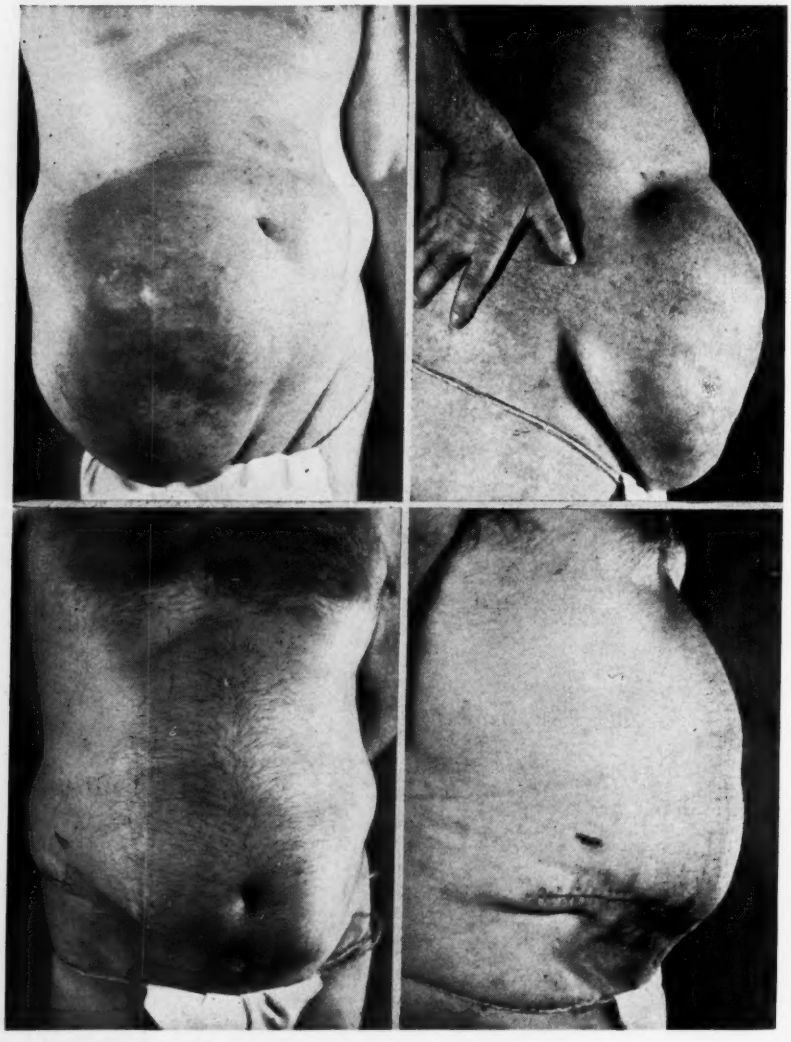
C D

FIG. 1.—Incisional hernia in a 56-year-old female following hysterectomy in 1932. Onset in 1933, previous attempt at repair elsewhere in 1935. Cutis graft repair September 30, 1944 (Case 8). (A) and (B). Front and side views before operation. (C) and (D). Front and side views six weeks after operation. The healed donor area on the right thigh is seen in (D).

Size and Description of the Hernia: In all instances the well-known fact that incisional hernia rings are smaller than they appear to be externally was demonstrated. However, rings 6x10, 6x13, 5x5, 9x9, 6x9, 9x11, and 13x13 cm.

were noted. All sacs came straight out or pointed to the right. In two cases two rings were noted. Representative herniae with results after operation are shown in Figures 1 and 2.

A B



C D

FIG. 2.—Incisional hernia in a 45-year-old male following appendicectomy, with drainage, elsewhere in 1940. Cutis graft repair February 28, 1945 (Case 11). (A) and (B). Front and side views before operation. (C) and (D) Front and side views four weeks after operation.

Anesthesia: In five cases gas-oxygen-ether was used alone, and in one case each was supplemented with pentothal and with spinal. In one case continuous spinal anesthesia was used.

Incision: In eight cases a transverse incision was used, in two, a vertical, and in one, the previous right subcostal incision was followed.

Source of Graft: The right thigh was used in ten cases and the part of the abdomen to be discarded after lipectomy was used in another case.

Associated Lipectomy: This was done in nine of ten cases where there is a statement in this regard.

Taking of the Cutis: This was done by three methods as follows:

(a) Dermatome flap method, used in Cases 1-5 and 7 and 8. This method is simpler and more rapid than any of the older technics. It is, however, more time-consuming than the two methods listed below. The under side of the cutis, being cut by hand with a scalpel, is of necessity irregular.

(b) Scola method, used in Case 6. This technic is rapid, but requires a very sharp blade and has the objection that it is difficult to cut the epidermis off the edges of the cutis, and this wastes a considerable portion of the graft.

(c) Split-split method, used in Cases 9-11. The quickest and most satisfactory method. (One of our dermatomes has an axle with considerable looseness and is not accurate enough to cut split-split grafts of any sort).

Thickness of the Epidermis: This varied from 9 to 20 thousandths of an inch, with an average of 13 thousandths in ten cases. The donor sites healed with no appreciable differences, as did the hernia wounds. A section of epidermis is shown in Figure 3.

Thickness of the Cutis: This can obviously be measured only when the Scola or split-split methods are used. In four cases it varied from 20 to 31 thousandths of an inch, averaging 24 thousandths. A section of cutis is shown in Figure 4.

Position of the Cutis Graft: In one case the cutis was placed right side up and in seven cases it was placed upside down (fat side up). In one instance (Case 7) a double thickness of folded cutis was used, the fat side being inside on each leaf. No difference in the results was noted. The reason for putting the nonfatty side down was the belief that it would unite more easily with the fascia beneath. A photograph of a patch of cutis sutured in place is shown in Figure 5.

Cultures: Cultures of the epidermis taken in four cases were all negative. These varied from the thinnest (0.009 inch) to the thickest (0.020 inch) slices of epidermis. In six cases the cutis was cultured and the results were negative in four instances (Cases 6, 7, 9 and 10). In two instances, as will be discussed later, the results were positive (Cases 8 and 11).

Closure of the Fascial Defect: This was transverse in five instances, vertical in five instances, and oblique in one instance. This corresponds to the skin incisions except that in three cases a transverse skin incision was followed by a vertical fascial closure. Transverse skin incisions were chosen because of the frequent desirability of lipectomy. Silk closure with interrupted sutures and, if possible, imbrocation of the fascial layers was used routinely. In no case did a fascial defect remain. In one case the anterior rectus sheath was split vertically on each side and folded over the suture line.

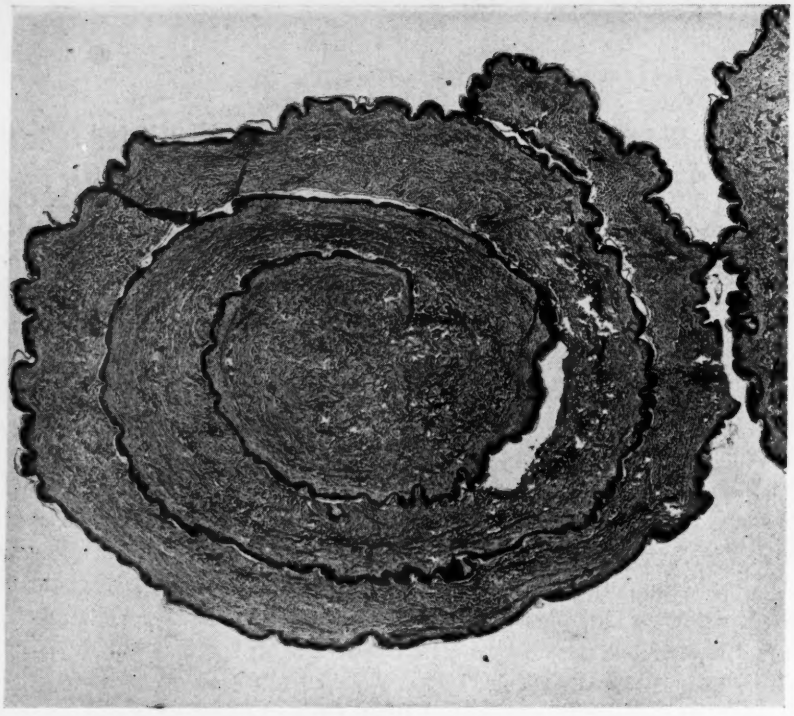


FIG. 3.—Discarded rolled-up epidermis in Case 10. The epidermis was removed at a depth of 0.020 inch by the split-split method from the portion of the abdominal wall to be discarded after lipectomy. Note the atrophic epidermis which could have been adequately removed by a more shallow excision.

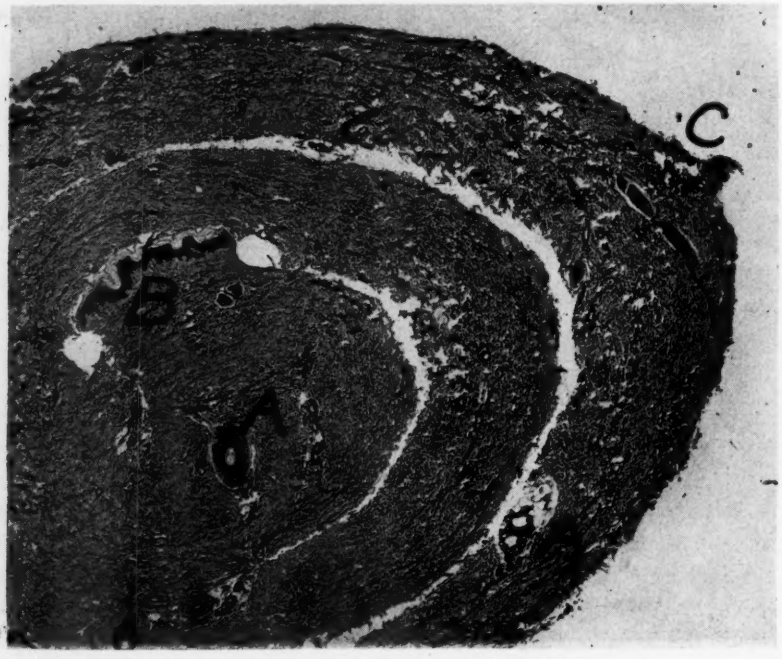


FIG. 4.—Portion of rolled-up cutis in Case 11. A full-thickness graft was removed at a depth of 0.040 inch (1 mm.) and the epidermis taken off by the split-split method at a depth of 0.014 inch, making the resultant cutis 0.026 inch thick. Note hair follicles and glands (A); border of epidermis (B) at edge of graft (such a border was removed from the piece of cutis that was buried); and an island of epidermis (C) which might have been overlooked and buried.

Histologic Examination: Sections of the epidermis removed in Case 10, at a depth of 20 thousandths of an inch, show that this depth of cutting was not necessary (Fig. 3). Sections of excess cutis in six cases all showed epithelial elements. This indicates that such an inclusion cannot be entirely avoided by cutting the epidermis deeper, unless the cutis itself is made so thin that it is of little value for supportive purposes.

Case 6.—Cutis: In a low power field several hair follicles and a few sebaceous and sudoriferous glands are identified. These occur at various depths in the cutis and are not just at the superficial edge. (Epidermis 0.009 inch; cutis 0.031 inch additional).

Case 7.—Cutis: Rather frequent hair follicles are seen at various depths in the cutis. One sebaceous gland, several sudoriferous glands and two epidermal pockets are identified. (Epidermis 0.012 inch; cutis cut by scalpel.)

Case 8.—Cutis: No hairs or hair follicles are seen, but there are numerous sudoriferous glands especially near the superficial surface of the cutis. These are, however, seen occasionally in the depths of the cutis. One sebaceous gland is identified and one patch of epidermis is seen in the surface; this latter is possibly the edge of a hair follicle. (Epidermis 0.011 inch; cutis cut by scalpel.)

Case 9.—Cutis: Few epithelial elements are present. The base of one hair follicle is seen at the outer surface and a few sudoriferous glands at various levels. No patches of epidermis or sebaceous glands are identified. (Epidermis 0.020 inch; cutis 0.020 inch additional.)

Case 10.—Cutis: There are few epidermal elements present, but one hair follicle and several sudoriferous glands are seen. (Epidermis 0.020 inch; cutis 0.020 inch additional.) It is of interest that this cutis as well as that from Case 9 both had the most (0.020 inch) epidermis removed, indicating that there is at least a quantitative reduction in the amount of epithelium left behind, even though there is not a qualitative disappearance of the same.

Case 11.—Cutis: Several hair follicles and glands are identified, as shown in Figure 4. At the edge of the cutis is a portion of unremoved epidermis. This remained attached because of rolling of the edge during the split-split process. The piece of epidermis was large enough to be visible to the naked eye and was removed from the portion of the cutis used for the operation. A smaller piece of epidermis near the center of the cutis was probably due to a glue blister on the dermatome. Such a piece might easily have been buried in the patient's wound. (Epidermis 0.014 inch; cutis 0.026 inch additional.)

Results: Ten of the 11 patients showed no recurrence of the hernia after the short follow-up of from one to 22 months (average eight months). All but one follow-up was by direct examination, the exception being by letter. Case 10 (weight 259 pounds) which at operation was more a diastasis than an hernia still has some diastasis at the upper end of the incision on straining. This patient and that in Case 9 still complain of a slight pain at one end of the incision. The other nine patients have no complaints referrable to the operation. The donor site is well healed in all but the patient in Case 5 who was last seen only one month after operation.

OBJECTIONS TO THE USE OF CUTIS GRAFTS IN THE REPAIR OF HERNIAE

These can be summarized as follows:

(1) ***Introduction of infection*** from bacteria contained in the hair follicles

and sudoriferous glands of the cutis. In published reports of clinical cases, infection does not seem to be a frequent postoperative complication. In Uihlein's series (1939) of 104 cutis graft operations, 15 wound infections (15 per cent) developed. The personal clinical cases cited above also substantiate this experience, there being only one case of wound infection (Case 11), and in this case the wound culture when the infection had developed (*hemolytic Staphylococcus albus*) did not reveal the same organism as did the cutis culture at the time of operation (heavy growth of *beta Streptococcus,* Lancefield Group B). The results of cutis cultures in the five other tested clinical cases were as follows: Negative in four cases and positive in Case 8 (moderate growth of *hemolytic Staphylococcus albus* and *Staphylococcus aureus*). In four cases, portions of the epidermis removed from the top of the cutis were cultured with no growth resulting in any instance.

The animal experiments described below were formulated to further test this aspect of the subject:

(2) *Persistence of Epithelial Elements with Resultant Cyst Formation:* Several writers, particularly Davis and Traut (1926), and Zimches (1931), have studied the effects of burying sheets of full-thickness skin in dogs. Cysts resulted after three to four weeks, and tended to persist. Peer and Paddock (1937) studied the effects of burying fragments of cutis in human beings, with histologic observations at intervals of from one week after operation. The cutis grafts were prepared by taking a Krause full-thickness skin graft from the abdomen. "The epidermis was shaved from each section as completely as possible with a sharp No. 11 Bard-Parker knife blade, and the remaining dermis and fat were inserted beneath the skin of the chest with the dermis outermost." This method did not yield a true cutis graft because the authors admitted and their sections demonstrated that "in spite of attempted complete removal of the epidermis, some epidermis remained." This gave rise to cysts containing horny material and some hairs. Sebaceous glands were noted only in the implants of one week's duration, hair follicles only up to three weeks, while sweat glands persisted for a year, but in later sections they were in the process of degeneration and fibrous replacement. The cutis grafts fused with the surrounding connective tissue, but the granulation tissue surrounding the implant was of the chronic inflammatory type with lymphocytes, macrophages, epithelioid cells, often giant cells, and in some cases granulomatous nodules. The latter contained elements resembling hairs in some instances.

The animal experiments described below were formulated to further test the importance of persistence of epithelial elements. Furthermore, since the advent of the dermatome, there is now a means of measuring accurately the exact depth of cutis used and epidermis removed, as was not the case in Peer and Paddock's experiments.

(3) *Bridging a Fascial Defect is Seldom Necessary in the Repair of Herniae:* This objection also holds for the use of fascial grafts. The author has never seen a ventral or incisional hernia where the fascial layers could

not be brought together. The cases of Scola (1944), where large defects in the fascia remained and these were covered with cutis, seem incomprehensible or are very rare. Swenson and Harkins (1943) reported that in recurrent inguinal herniae silk gives just as good if not better results than fascia. The indication for cutis would seem to be, therefore, as a reinforcement of an already carefully executed silk (or other nonabsorbable material) repair.

(4) *Reinforcement is not Necessary in Small Herniae and Increases the already Long Operating Time too much in Large Herniae.* This objection is valid in many cases, but, on the other hand, a large group of moderate sized herniae do appear to be better supported with a reinforcing patch of cutis. When the cutis is taken by the split-split method, the additional time required is about 20 minutes. When one of the combined dermatome-manual technics is used, up to 50 minutes may be consumed in taking and applying the graft and in suturing the donor site. When two teams are available, this additional time can be cut down to almost nothing. The amount of blood lost by the additional procedure is, on the other hand, quite small.

EXPERIMENTAL STUDIES

Cutis grafts were implanted in 25 experiments upon 14 dogs. The grafts were taken by the various methods outlined in discussion of the clinical cases and sections and cultures were made of the epidermis and of the cutis. Necropsy studies were made as to the gross and histologic fate of the grafts. All experiments were undertaken under ether anesthesia, and with routine aseptic technic.

Experiment 1.—(Dog 1, female, 9.8 Kg.) October 16, 1944. *Abdominal Wall Implant:* A piece of cutis 4 cm. square was removed from beneath a dermatome graft of 0.014 inch with a scalpel and was implanted over the rectus sheath on the right side with the epidermal side up. Death occurred on the 22nd day from no apparent cause and necropsy showed no definite wound infection. There were no evident gross cysts, but histologic section revealed numerous horny clusters separated from the rectus sheath by a fatty layer.

Experiment 2.—(Dog 1) *Abdominal Wall Implant:* A similar graft was placed epidermal side down on the left rectus sheath. Gross cysts were present at necropsy and histologic examination (Fig. 6) revealed a picture similar to that in Experiment 1, except that the horny clusters pointed towards the rectus sheath rather than away from it.

Experiment 3.—(Dog 2, female, 10.2 Kg.) October 23, 1944. *Abdominal Wall Implant:* A small cutis graft similar to those in Experiments 1 and 2 was placed over the muscular fascia of the lower lumbar region with the epidermis down. The wound was well healed, as was the donor area, on September 21, 1945 (11 months) when the animal which was in good shape was sacrificed. The graft was still present, clean, and was fused with the surrounding tissues. Histologic section revealed hairs, small epithelial-lined cysts, and clusters of epithelial cells, all with practically no sign of surrounding inflammatory reaction.

Experiment 4.—(Dog 2) *Abdominal Wall Implant:* A similar graft was placed in the upper lumbar region with the epidermis up. The wound is well healed and the graft clean and similar to that in Experiment 3 except that it was less demarcated from the surrounding tissue on necropsy. Histologic section revealed numerous but scattered hairs and hair roots with no sign of surrounding inflammatory reaction.

Experiment 5.—(Dog 3, female, 9.5 Kg.) November 15, 1944. *Iliac Artery Ligation:* A cutis graft was removed with a scalpel from the back after taking off the

epidermis at a depth of 0.010 inch by the dermatome flap method. The epidermis shows numerous transected hair follicles as seen in Figure 7. Numerous hairs and glands were present throughout the cutis and, in fact, were quite numerous in the fatty tissue beneath it as seen in Figure 8. The number of epithelial elements was much larger than in the human cases (Fig. 4). Two strips of cutis were used to ligate the right common iliac artery twice. Death occurred from inanition without gross wound infection on April 9, 1945 (five months). The artery was occluded, but considerable sebaceous material was about the site of the ligature.

FIG. 5.—Cutis graft (the white patch in the wound bed) in place (Case 1). The cutis graft was taken from the right thigh by the dermatome flap method and is used as a patch over the suture line of a modified Mayo-type repair of an incisional hernia. This hernia occurred in a male 40 years of age, and was situated in the right subcostal region following a cholecystectomy in 1940. One previous attempt at repair had been made elsewhere.

Experiment 6.—(Dog 3) *Abdominal Wall Implant:* A large piece of the cutis (9 x 4 cm.) graft was placed over the right rectus sheath with the epidermal side down. At necropsy, this graft was not completely adherent to the rectus sheath.

Experiment 7.—(Dog 3) *Abdominal Wall Implant:* A smaller piece of the cutis placed over the left rectus with the epidermal side up was well healed and scarred at necropsy, but histologic sections showed hairs and chronic granulation tissue.

Experiment 8.—(Dog 3) *Abdominal Wall Implant:* A small piece of cutis was placed between the peritoneum and the properitoneal fat with the epidermal side towards the peritoneum. At necropsy, it was puckered and sebaceous-like material was grossly present.

Experiment 9.—(Dog 4, female, 11.8 Kg.) November 20, 1944. *Iliac Artery Ligation:* A cutis graft was obtained from the back by the split-split method (epidermis 0.008 inch, and cutis 0.032 inch additional). Hairs and attached sebaceous glands as well as sudoriferous glands made up a good portion of sections of the cutis. These were just as plentiful in the middle of the cutis as on its superficial edge, but less so at its deep margin. The left common iliac artery was tied with two strips of cutis 1 cm. wide. It tied more easily than when the cutis was cut by hand (Experiment 5). The lumen of the iliac artery was quite intact and no remnant of the cutis was found when the dog was sacrificed on June 27, 1945 (seven months).

Experiment 10.—(Dog 4) *Abdominal Wall Implant:* A portion of cutis was placed under the left external oblique over the celiotomy suture line with the epidermal side out. At necropsy, a sinus came from this wound, and there was a large collection of hairs at the site of the graft, with acute infection demonstrated grossly and microscopically. There was no weakness of the abdominal wall.

Experiment 11.—(Dog 4) *Abdominal Wall Implant:* A piece of cutis was placed over the left external oblique in the upper abdomen with the epidermal side in. It was not adherent at necropsy to the external oblique, but was to the subcuticular structures. Hair, sebaceous material and granulation tissue were present, grossly and microscopically.

Experiment 12.—(Dog 5, male) November 20, 1944. *Abdominal Wall Implant:* A cutis graft was obtained from the chest by the split-split method (epidermis 0.016 inch, and cutis 0.024 inch additional) and placed epidermal side down over the right external oblique. A piece of the epidermis when sectioned showed transected hair follicles as did the cutis strip. The animal died from pneumonia on the seventh day. The wounds on the right side were infected (see also Experiment 14) but were not on the left (see Experiment 13). The cutis seemed to be attached, however.

Experiment 13.—(Dog 5) *Abdominal Wall Implant, Double Thickness:* Another strip of cutis was sutured after folding it double with the epidermal side inside beneath the left external oblique. At necropsy this graft was clean and no infection or sebaceous material was noted grossly. Microscopically, a small abscess, 0.5 x 4.0 mm., containing polymorphonuclear neutrophils was present as well as sebaceous material and hairs.

Experiment 14.—(Dog 5) *Homologous Graft, Abdominal Wall Implant, Double Thickness:* A piece of cutis obtained from another dog that died from anesthesia, and taken by the same technic, was placed without suturing over the right external oblique after folding double with the epidermal side out. At necropsy this graft was infected, but firmly attached.

Experiment 15.—(Dog 6, female, 10.5 Kg.) November 27, 1945. *Abdominal Wall Implant, Rolled Up:* A cutis graft 8 x 11 cm. was taken from the lower chest by the split-split method (epidermis 0.020 inch, and cutis 0.020 inch additional). Half of this was rolled up with the epidermal side outside under the skin of the right groin through a midline incision. Sections of epidermis and cutis were similar to those in Figures 7 and 8. The animal was sacrificed June 27, 1945 (seven months). The wound was clean and no evidence was found of the cutis graft. The donor area to which the epidermis had been resutured was well healed, but practically hairless.

Experiment 16.—(Dog 6) *Abdominal Wall Defect:* The other piece of cutis fell on the floor, but was washed in saline and was sutured in a 10 x 3 cm. excised defect of the left lower abdominal musculature (oblique muscles and rectus abdominus) against the transversalis muscle and peritoneum with the epidermal side down. At necropsy the graft was well fixed and clean. Sections showed no sign of infection or epithelial

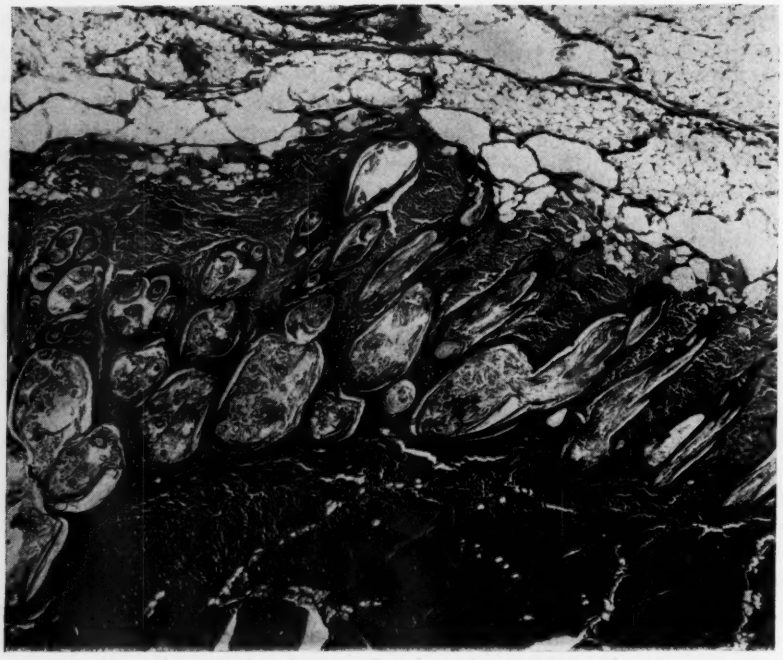


FIG. 6.—Necropsy specimen of cutis graft from Dog 1, taken 22 days after operation. The graft was placed upside down on the rectus abdominis muscle. Note the numerous horny nests.

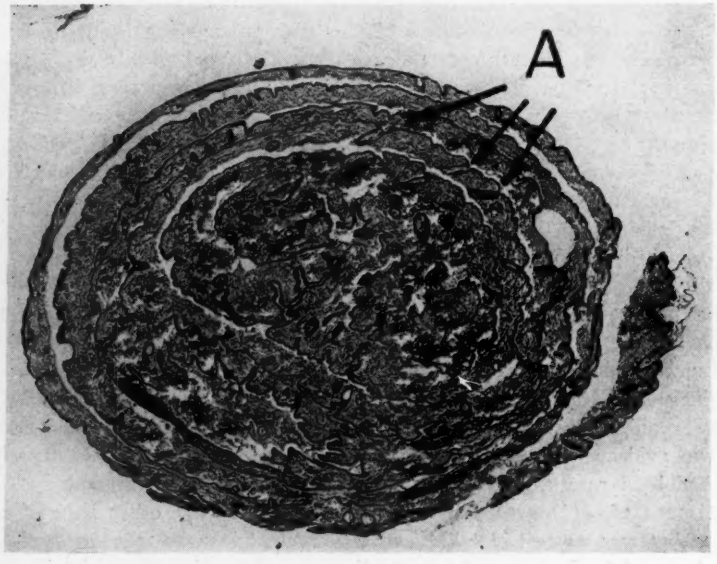


FIG. 7.—Rolled-up epidermis from Dog 3, taken at a depth of 0.010 inch. Note the numerous bisected hair follicles, some of which are seen at (A).

remnants and only traces of hemosiderin deposits. Sections of the donor area to which the unused epidermis had been regrafted showed essentially normal skin.

Experiment 17.—(Dog 7, female, 9.8 Kg.) *Aortic Ligation:* A cutis graft 8 x 12 cm. was taken from the chest by the split-split method (epidermis 0.020 inch, and cutis 0.020 inch additional). Marcks' copper gauges were used to measure the thickness of the grafts in this and in ensuing experiments. Sections of epidermis and cutis were similar to those in Figures 7 and 8. Three strips 1 x 12 cm. were used to ligate the

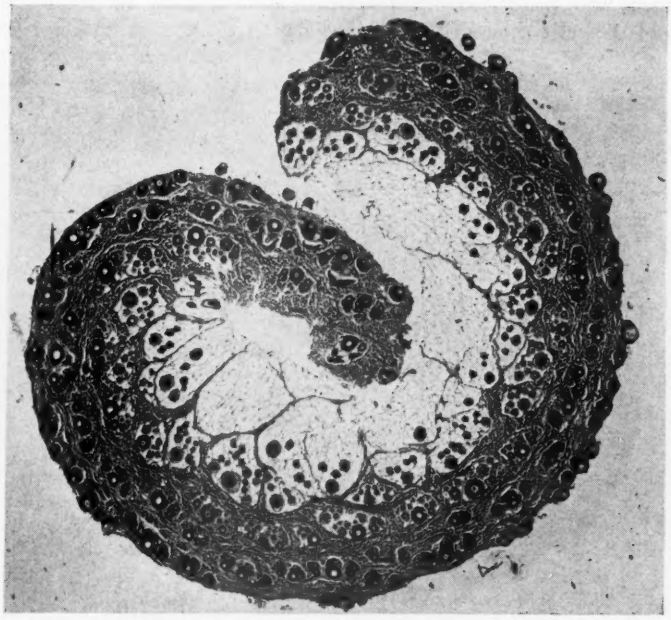


FIG. 8.—Rolled-up cutis graft from Dog 3. The epidermis was removed at a depth of 0.014 inch, and the cutis removed from the underlying bed with a scalpel. Note the large number of epithelial elements as compared to the human case seen in Figure 4.

abdominal aorta. A triple tie was used in each case and the knots were transfixed with one silk suture which did not surround the aorta. On the twelfth day the animal died of distemper. The donor area to which the epidermis had been resutured was entirely healed. All wounds were healed and clean. The aortic ligatures had atrophied and the lumen was reduced by only one-third.

Experiment 18.—(Dog 7) *Abdominal Wall Defect:* A 2.5 x 7.5 cm. area of oblique muscles was excised and the remainder of the cutis graft was fastened with interrupted silk sutures in place, epidermal side down, over the transversalis muscle. At necropsy, the graft was clean and was quite adherent on its lower (epidermal) surface, but not quite on its upper surface. A section of the cutis shown in Figure 9 demonstrates good fusion to the surrounding structures, but with contained epithelial elements including hair follicles. A section of the grafted donor area shows the graft viable and united with the underlying structures by a thin zone of granulation tissue. Sections of the abdominal wall showed the muscle quite adherent to the underlying internal oblique. A moderate number of hairs and hair follicles were fused with the surrounding tissue. Round cells were seen but no polymorphonuclear neutrophile collections were found.

Experiment 19.—(Dog 8, female, 7.7 Kg.) January 15, 1945. *Aortic Ligation:* Two strips of cutis 1 cm. wide obtained by the split-split method from the chest (epidermis 0.020 inch, and cutis 0.020 inch additional) were used for ligatures of the abdominal aorta. The knots were sutured with silk to prevent slipping but the silk

did not surround the aorta. The animal died of distemper on the 17th day. The aortic lumen was not reduced. The cutis had degenerated into a mass of sebaceous material about 12 mm. in diameter. No true pus was present. The donor areas to which the epidermis had been resutured were entirely healed.

Experiment 20.—(Dog 9, female) March 5, 1945. *Abdominal Wall Defect:* A cutis graft obtained by the split-split method from the upper abdomen (epidermis 0.020 inch, and cutis 0.020 inch additional) was sutured in a defect of the entire thickness of the abdominal wall below the subcutaneous tissue measuring 2.5 x 7.5 cm. Sections of a portion of the cutis showed it to be irregular in thickness with one side composed

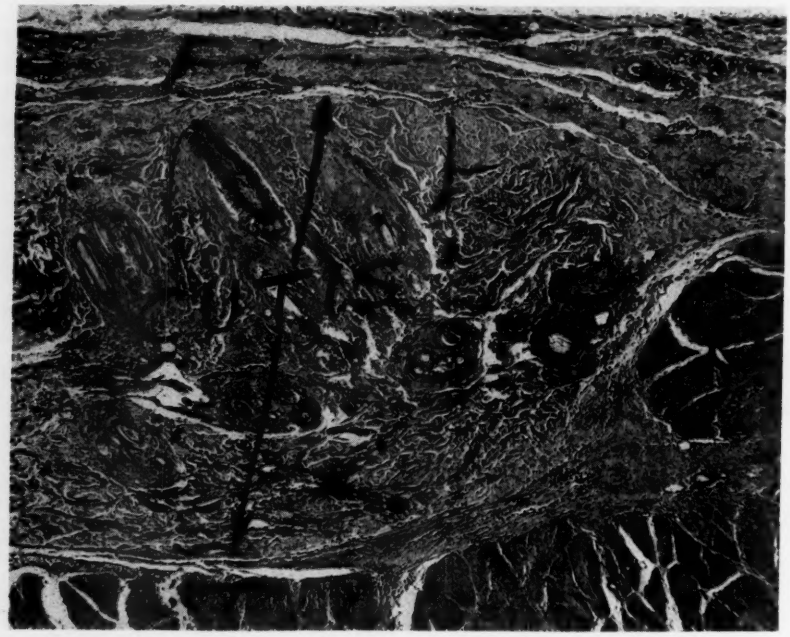


FIG. 9.—Cutis graft in place at necropsy 12 days after operation in Dog 7. A strip of cutis was obtained from a full-thickness graft of 0.040 inch by splitting it in two by the split-split method and utilizing the deeper half. An area of external and internal oblique muscles, 3 × 1 inches, was excised and the strip of cutis fastened upside down on the transversalis muscle (T). The cutis lies beneath the superficial fascia (F) and joins the oblique muscles (O) on the right. It contains epithelial elements, including hair follicles.

mainly of fat and containing practically no epithelial elements while the other side contained many hair roots and some hairs. The graft was sutured to the cut edges of the surrounding muscles with the epidermal side facing the intestines. The donor site to which the epidermis was resutured was entirely healed in one month. At the time of sacrifice on September 21, 1945 (6.5 months) the animal was in excellent condition and there was no sign of hernia. All wounds were well healed. Histologic section of the donor skin grafted area showed good epithelium with hairs and other accessory epithelial elements. A surrounding edge of second degree scar-healing showed a thin layer of epithelium with very few hairs. The graft was firm, but not as strong as the surrounding tissues and had shrunk to a size of 7.0 by 2.5 cm. Histologic section of the cutis graft scar showed many small cysts containing hairs and epithelial buds.

Experiment 21.—(Dog 10, female) March 12, 1945. *Abdominal Wall Defect:* This was exactly similar to the preceding experiment except that the epidermal thickness was 0.018 inch, and the cutis 0.022 inch, and the cutis was placed epidermal side out in the abdominal wall. Sections of a portion of the cutis showed it to be mainly fat. Few epithelial elements were present and these included hairs, hair roots, and one demon-

strable sudoriferous gland. The animal was found dead on April 4, 1945 (23 days) with minimal distemper. The donor site was only 50 per cent healed. The cutis graft was well healed and clean. The defect had shrunk to 3 x 6 cm. Sections showed that the graft was of poor quality containing considerable fat, a very occasional hair but no other epithelial elements. One small collection of polymorphonuclear neutrophils lay beneath the skin at the edge of the graft but superficial to it.

Experiment 22.—(Dog 11, female) March 21, 1945. *Diaphragmatic Defect:* A cutis graft of a thickness similar to that of the last experiment was taken from the abdomen and sutured into a full-thickness excised defect in the left diaphragm through a transthoracic approach with the epidermal side towards the chest. Sections of a portion of the cutis revealed a thin layer of muscle with fat on each side and with no epithelial elements. On July 19, 1945 (four months) the dog was well, the donor site was well healed and the wound was clean. Death occurred on August 28, 1945. Necropsy was not performed.

Experiment 23.—(Dog 12, female, 4.5 Kg.) March 28, 1945. *Abdominal Wall Defect:* A cutis graft of thickness similar to that in the last two experiments was taken from the upper abdomen and sutured into a whole-thickness defect of the abdominal wall musculature about 2.5 x 9 cm. Sections of the graft showed it to be very uneven in thickness. In one place it had practically no cutaneous elements, in another a great many. The graft was folded double with the epidermal layer inside facing itself. The animal was sacrificed on June 27, 1945. The donor area was entirely healed. The abdominal wound was entirely clean and healed and represented a perfect result. There was no weakness. The defect measured 3 x 9 cm. The intestines were not adherent to the underside of the graft but the omentum was slightly attached. The graft was well adherent in its upper surface. Histologic section showed a thick layer of relatively normal fibrous tissue containing very occasional hairs.

Experiment 24.—(Dog 13, female, 5.2 Kg.) March 29, 1945. *Diaphragmatic Defect:* A cutis graft taken from the abdomen by the split-split method (epidermis 0.014 inch, and cutis 0.026 inch additional) was sutured to a 2.5 x 4 cm. defect in the diaphragm with the epidermal side towards the chest. The animal died in four hours, and at necropsy the graft was seen to be quite intact.

Experiment 25.—(Dog 14, female, 6.0 Kg.) April 2, 1945. *Diaphragmatic Defect:* A graft similar to that in Experiment 24 was sutured to a diaphragmatic defect 4 x 6 cm. with the epidermal side towards the chest. The animal was sacrificed on June 27, 1945 (2.5 months). The donor site was entirely healed and the chest wound was clean. The graft was intact without weakness and was firmly attached to the lung and only partially attached to the liver. Sections of the cutis at the time of operation were similar to Figure 8 except that epithelial elements were not so widely distributed. Histologic examination of the graft at necropsy revealed an intact graft firmly adherent to the underlying lung and in places adherent to the liver. The graft contained a few hairs and hair roots and sebaceous cysts 0.5 mm. or less in diameter. No notable signs of inflammation were present. Sections of the donor site revealed an intact but thin epithelium with hairs and underlying glands.

RESULTS OF CULTURES

Aerobic and anaerobic cultures of the cutis obtained from the first five dogs all showed only a gram-positive anaerobic gas-forming bacillus with no spore formation or branching. In one case (Dog 3) where incidentally only a thin (0.010 inch) layer of epidermis was removed, an additional growth of *Staphylococcus aureus* was observed. At necropsy the wounds of Dogs 4 and 5 were grossly infected.

ANALYSIS OF EXPERIMENTAL DATA

A total of 25 experiments on 14 dogs included 13 abdominal implants, five bridging of abdominal wall defects, two ligations of the common iliac artery, two ligations of the abdominal aorta, and three bridging of diaphragmatic defects.

In the series of 13 abdominal wall implants at various levels and positions, all examined at necropsy, no remnant of the graft was found in one case, granulation tissue or pus was found four times, gross hairs in two instances, gross sebaceous material in two instances, sinuses once, and apparently clean healing six times. In eight experiments histologic sections were made and all revealed epithelial elements including two in which no gross hairs were evident. In 12 instances where fusion of the graft to surrounding surfaces could be noted, fusion was present on both surfaces eight times, on the fat side but not on the epidermal side of the graft twice, and the graft was not adherent at all in two instances. Of the 13 grafts observed, only six were without some complication (pus, hair, sebaceous material, entire disappearance of the graft, *etc.*).

In the series of five bridging of abdominal wall implants, all examined at necropsy, on gross examination all showed complete absence of hair, pus, cysts, *etc.*, Three grafts were adherent on both surfaces and one on the epidermal surface only. Histologically, hair was present four times and absent once.

In the series of two common iliac ligations, in one there was no remnant of the graft and no occlusion of the artery, and in the other the artery was occluded, but a mass of sebaceous material was present.

In the series of two aortic ligations, in neither case was the aorta occluded. In one the graft had disappeared, in the other a sebaceous mass was present.

In the series of three diaphragmatic defects of two animals examined at necropsy no gross evidence of abnormal healing was observed (one animal, Experiment 24, died after only four hours; the other, Experiment 25, was sacrificed after 2.5 months). The graft was adherent mainly on its epidermal surface in Experiment 25, and sections in this case revealed hairs and sebaceous cysts.

NOTE ON THE USE OF WHOLE SKIN AS A SUBSTITUTE FOR FASCIA (AND FOR CUTIS)

In the January, 1945, issue of the British Journal of Surgery an article by Mair of Aberdeen, Scotland, appeared on the use of whole skin grafts as buried patches for the repair of hernia. This author reports the use of this method in 88 herniae, and studied the results of whole skin implants in rabbits. This same author has another article in a recent issue of the American Journal of Surgery. Despite the excellent results reported with this method, it would appear to be more risky than the use of cutis, but these articles deserve reading. It would seem that while one layer of cutis might be weaker than one layer of whole skin, two layers of cutis would

be stronger and still not have as many epithelial elements combined as the single layer of skin.

SUMMARY

A cutis graft reinforcement patch was used in the surgical repair of 11 cases of large ventral or incisional herniae. These herniae were in most instances chosen for this type of repair because of their large size and associated obesity of the patient. Seven cases were specifically selected from a large number of ward patients because of the magnitude of the hernia.

In all cases the fascial layers were closed with silk sutures and the cutis acted only as a supportive patch. The cutis was obtained by four methods: (1) Dermatome flap; (2) Scola double graft; (3) split-split; and (4) from tissue removed from the region of the hernia by lipectomy. In all cases, except when the fourth method rendered it unnecessary, the donor area was again covered with the removed epidermis.

The results of the operation were completely satisfactory in all but one instance (Case 10). In this instance some diastasis of the upper end of the wound recurred. It is impossible to state, however, that the basic silk repair, often by the Mayo technic with imbrocation, might not have been equally satisfactory and that the cutis graft was superfluous.

The chief objections to use of cutis grafts have been met in these clinical cases as follows: (1) Infection with drainage occurred in only one wound, and in that instance was associated with finding a different organism from that cultured from the cutis at the time of operation. (2) Cyst formation from persistent epithelial elements has to date caused no obvious trouble in any case. (3) Increased operating time has been largely obviated by use of the split-split method.

Variations in the technic whereby single and double layers of cutis were used; whereby in different cases the cutis was placed epidermal side down (seven instances) and epidermal side up (one instance); whereby the thickness of the removed epidermis and of the cutis itself was varied, all seemed to have no effect on the results.

While the results of the human cases were in general quite satisfactory, the animal experiments were accompanied by a high incidence of complications. In all cases but one of the 14 where sections of the buried graft were taken at necropsy, epithelial elements were present. Pus, hair, sebaceous material, or sinuses were observed in 18 out of 24 experiments (75 per cent) in which the graft was observed at necropsy. In four other instances no epithelial remnant of the graft was found and in the two remaining cases the intact graft was observed. Most of these complications followed the insertion of the cutis as abdominal implants or its use as arterial ligatures. The experiments where the graft was actually sutured under tension to close muscular defects in the abdominal wall or diaphragm were much better, with no gross complications of healing being observed in six such experiments.

Ligations of the abdominal aorta and common iliac arteries were not successful with cutis strips. Either the artery was not occluded or the cutis

degenerated into sebaceous material. The reëstablishment of continuity of the arterial lumen is possibly attributable to the elasticity of the cutis.

The difference between the human and animal experiments would seem to be a quantitative rather than a qualitative one. It is impossible to remove all of the epithelial elements from the cutis without excising such a thick layer of epidermis that no dermis is left behind. It was one of the initial hopes of this investigation that with the modern precise methods of taking grafts at known depths the optimum thickness of cutis and of removed epidermis might be ascertained. Actually, it seems to make little difference because once the superficial epidermis is shaved off—and this can be done by a very shallow setting of the dermatome (0.008 inch, or even less)—the epithelial elements in the underlying cutis penetrate deeply. It is true that quantitatively the deeper one removes the epidermis the less the remaining cutaneous remnants, but also the less the remaining cutis. This quantitative difference is especially noticeable in the animal experiments where a large amount of epithelial material in the cutis (estimated histologically in area as 50 times as much, or more, in a section of cutis of equal size) is far greater than in a human cutis graft.

CONCLUSIONS

1. Quantitative studies on cutis grafts cut at various thicknesses indicate that superficial removal of the epidermis need be no more than 0.008 inch.

2. A relatively nonhairy donor site is desirable to avoid as much as possible the inclusion of hair follicles and attached glands. The danger of such an inclusion is essentially quantitative rather than qualitative, but is always to be considered. With adequate skin preparation infection does not seem to be a major menace.

3. The split-split method is the most useful technic for obtaining cutis grafts.

4. It seems to make little difference whether the cutis is used with the epidermal side up or down, or whether it is inserted in single or double sheets.

5. Cutis grafts should be applied under tension and when used in the surgical treatment of hernia should be fastened as a supporting patch over the suture line of an otherwise adequate repair of the fascial layers with nonabsorbable sutures.

6. Cutis grafts as used in these experiments are not suitable for ligation of major arteries.

BIBLIOGRAPHY

[1] Cannaday, J. E.: The Use of the Cutis Graft in the Repair of Certain Types of Incisional Herniae and Other Conditions. ANNALS OF SURGERY, 115, 775–781, May, 1942.

[2] Cannaday, J. E.: Some of the Uses of Cutis Graft in Surgery. Am. J. Surg., 59, 409–419, February, 1943.

[3] Cannaday, J. E.: Personal communication, December 29, 1944.

4 Davis, J. S., and Traut, H. F.: The Production of Epithelial-lined Tubes and Sacs. J. A. M. A., **86,** 339, January 30, 1926.

5 Loewe, O.: Über Hautimplantation an Stelle der Freien Faszienplastik. München. med. Wchnschr., **60,** 1320–1321, June 17, 1913.

6 Loewe, O.: Uber Haut-Tiefenplastik. Munchen. med. Wchnschr., **76,** 2125–2128, December 20, 1929.

7 Mair, G. B.: Preliminary Report on the Use of Whole Skin-grafts as a Substitute for Fascial Sutures in the Treatment of Herniae. Brit. J. Surg., **32,** 381–385, January, 1945.

8 Mair, G. B.: Use of Whole Skin Grafts as a Substitute for Fascial Sutures in the Treatment of Herniae: Preliminary Report. Am. J. Surg., **69,** 352–365, September, 1945.

9 Peer, L. A., and Paddock, R.: Histologic Studies on the Fate of Deeply Implanted Dermal Grafts: Observations on Sections of Implants Buried from One Week to One Year. Arch. J. Surg., **34,** 268–290, February, 1937.

10 Rehn, E.: Das kutane und subkutane Bindegewebe als plastisches Material. München. med. Wschnschr., **61,** 118–121, January 20, 1914.

11 Scola, J. V.: Improved Technic for Preparing a Buried Dermal Graft in Hernial Repair. Am. J. Surg., **66,** 249–251, November, 1944; *idem:* Bull. New York Acad. Med., **21,** 439, August, 1945.

12 Straatsma, C. R.: Use of Dermal Graft in Repair of Small Saddle Defects of the Nose. Arch. Otolaryngol. **16,** 506–509, October, 1932.

13 Swenson, S. A., Jr., and Harkins, H. N.: Cutis Grafts: Application of the Dermatome-flap Method: Its Use in a Case of Recurrent Incisional Hernia. Arch. Surg., **47,** 564–570, December, 1943.

14 Swenson, S. A., Jr., and Harkins, H. N.: The Surgical Treatment of Recurrent Inguinal Hernia: With Special Reference to a Cooper's Ligament Herniotomy and the Use of Free Fascial Grafts. Surgery, **14,** 807–818, December, 1943.

15 Uihlein, A., Jr.: Use of the Cutis Graft in Plastic Operations. Arch. Surg., **38,** 118–130, January, 1939.

16 Zimches, J. L.: Frankfurt. Ztschr. f. Path., **42,** 203, 1931: Cited by Peer and Paddock,[9] 1937.

17 Zintel, H. A.: Resplitting Split-thickness Grafts with the Dermatome: A Method for Increasing the Yield of Limited Donor Sites. ANNALS OF SURGERY, **121,** 1–5, January, 1945.

THE PATHOGENESIS OF LOCALIZED FIBROUS LESIONS IN THE METAPHYSES OF LONG BONES

C. Howard Hatcher, M.D.
Chicago, Ill.

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF CHICAGO, DIVISION OF ORTHOPEDIC SURGERY, CHICAGO, ILL.

Localized benign fibrous lesions which are situated in the metaphyses of long bones have been described under a variety of diagnoses. The diverse interpretations accorded examples of this disorder have been due mainly to overemphasis on various secondary characters prominent in the natural course of the condition. Phélip,[1] and Burman and Sinberg,[2] among other described typical examples of this fibrous lesion as solitary xanthoma, not recognizing that the lipoid accumulation was a secondary manifestation. Superficial resemblance of the fibrous lesions to solitary bone cyst and to benign giant cell tumor led Geschickter and Copeland[3] to interpret them as variants of these disorders. Phemister,[4] in 1929, reported on the pathologic characteristics of a group of localized, nonsuppurative lesions of bone which he termed fibrous osteomyelitis. Included in his cases were instances of the lesion now identified as osteoid osteoma as well as examples of metaphyseal fibrous defects. In 1942, Jaffe and Lichtenstein[5] demonstrated the various stages in development of solitary fibrous lesions of bone, interpreted them as benign tumors formed from matured marrow connective tissue and applied the name nonosteogenic fibroma of bone.

The purpose of this presentation is to demonstrate the clinical, roentgenologic and pathologic findings in the various stages of the lesion's development and regression. Attention is brought to the frequency with which evidence of concomitant disturbances in epiphyseal cartilage and in bone are observed. The significance of this observation in the pathogenesis of the fibrous metaphyseal lesion is discussed. The basis for this report is the study of 45 patients in whom were identified 51 lesions of the type under discussion. Lesions were found in more than one bone in five patients. There are 28 males and 17 females in the group. That the disorder has its inception during the period of longitudinal growth of bone is indicated by the fact that all except seven patients were children at the time of recognition of the abnormality. The defects in the bones of adult patients showed roentgenographic evidence indicative of long duration of the disorder. The youngest patient who had a metaphyseal defect was six years, and the oldest was 40 years at the time diagnosis was made.

In all these cases the lesion was in the long bones of the lower extremities. Jaffe and Lichtenstein found in ten cases one with localization in the distal end of the ulna. In the present group the lesions are distributed in the skeleton as follows: Thirty-two in the distal portion of the femur; 11 in the proximal portion of the tibia; five in the distal metaphysis of the tibia; and

two in the distal third of the fibula. All of them are situated in the metaphysis or adjacent shaft where they are usually eccentrically placed. The defect often abuts on the cortex or occupies a portion of it.

A typical example of a metaphyseal fibrous defect, illustrating its eccentric location in the distal end of the femur, is seen in the following case:

Case 1.—E. S., male, age 17, had recurrent attacks of pain in the left knee for 1.5 years. Examination showed evidence of fluid within the knee joint and localized tenderness mesially over the distal end of the femur. Roentgenograms (Fig. 1) show a zone

FIG. 1.—Case 1: Roentgenograms show area of reduced density mesially in the metaphysis of femur.

of reduced density mesially in the metaphysis which occupies a portion of the cortex. It is demarcated from surrounding bone by a narrow scalloped sclerotic margin. Bloc excision of this focus was done. The specimen (Fig. 2) presented as a fibrous mass with brownish discoloration, occupying a smooth-walled cavity in the bone. The outer cover of the cavity is periosteum which blends into the fibrous tissue of the focus. A slight amount of periosteal new bone is present here. Microscopic examination (Fig. 3) discloses whorls and strands of fibrous tissue with small areas of recent hemorrhage and blood pigment deposition. Scattered multinucleated cells are found; also, in some areas, lipoid-containing macrophages are observed. The bony wall shows evidence of bone absorption in some regions; in others, bone apposition is apparent. There is no ossification within the fibrous mass. The zone of reactive bone about the focus is narrow and the surrounding marrow is normal. The patient's symptoms were relieved by operation, and he is well, four years later.

In five patients there were lesions in more than one bone. Two had defects in the tibia and femur of the same extremity. One had lesions in both femora and in one tibia. Both tibiae were involved in one case and both femora in another. Although the lesion is unilocular there are occasionally seen smaller separate adjacent foci.

Involvement of more than one bone is illustrated in the following two cases:

Case 2.—C. C., female, age ten, had pain, tenderness, and slight swelling over the left tibial tubercle for two weeks. A clinical diagnosis of Osgood-Schlatter's disease was made. Roentgenograms (Fig. 4) show an area of reduced density with marginal sclerosis in the distal portion of each femur and in the proximal end of the right tibia. The one in the right tibia is close to the epiphyseal disk. In the right femur the lesion is in the shaft, further from the growth disk, and has greater sclerosis about it. The lateral

FIG. 2.—Case 1.—Photograph of bloc shows defect in cortex filled with fibrous tissue.

cortex of the left femoral metaphysis is the site of a smaller lesion. The left tibial tubercle is of irregular density. The symptoms in this patient were connected with changes in the tibial tubercle. The metaphyseal foci caused no pain and no treatment was given them.

Case 3.—N. W., female, age 11, had tuberculosis of the right hip for which arthrodesis was done at the age of four years. There were no symptoms referable to the knees. Roentgenograms of both knees were made for examination of the epiphyseal cartilage disks because of limb length inequality. These roentgenograms (Fig. 5) disclose an area of rarefaction in the proximal metaphysis of each tibia. That in the left tibia borders on the epiphyseal cartilage. In the right tibia a similar area is situated further from the epiphyseal line and encroaches upon the medial cortex.

The symptoms produced by this defect are usually mild. In several instances its presence was discovered in roentgenograms made because of recent injury to the limb. Pain, when present, is mild, intermittent, and often referred to the neighboring joint. Local tenderness over the involved area is present when the lesion lies in, or close to, the cortex. Symptoms and

physical findings of epiphyseal disturbances led to the discovery of the associated metaphyseal disorder in 14 patients.

ROENTGENOGRAPHIC APPEARANCE

The roentgenographic appearance of the metaphyseal defect is distinctive, and in conjunction with clinical findings diagnosis can be made with considerable certainty. Early, there is a limited area of reduced density in the meta-

FIG. 3.—Case 1: Photomicrograph shows whorls and strands of fibrous tissue with scattered multinucleated cells.

physis close to the epiphyseal disc. Later, the area is apt to be elongated in the direction of the axis of the bone and show sharp demarcation from surrounding normal bone by a narrow shell of bone sclerosis. Irregularly scalloped margins give the appearance of loculation on the roentgenograms. Through longitudinal growth of the bone the defect comes to lie further from the epiphyseal cartilage. Also, in the process of tubulation of the metaphysis the defect may eventually occupy a part of the cortex of the bone. In this case periosteal reaction may produce the shadow of overlying periosteal new bone. In lesions long present there may be roentgenographic evidence of progressive ossification at the periphery, with resulting marginal sclerosis several millimeters in width. Sometimes dense ossification may fill out part or all of the area, leaving a zone of increased density in the roentgenogram.

FIG. 4.—Case 2: Roentgenograms show an area of reduced density with marginal sclerosis in the right femoral as well as tibial metaphysis. In the left femur a smaller area lies in the lateral cortex.

PATHOLOGY

Surgical removal of the lesion was done by curetting or by bloc excision in 17 of the patients. This material afforded means for study of the histologic nature of the process at various stages.

The pathologic appearance, like the roentgenographic, varies somewhat

FIG. 5.—Case 3: Roentgenograms show areas of reduced density in both tibial metaphyses. That in the left tibia borders on the shadow of epiphyseal cartilage. In the right tibia it encroaches upon the shadow of the mesial cortex.

FIG. 6.—Case 4: Roentgenograms show ovoid area of reduced density which expands shaft of fibula.

with the age and activity of the lesion, and different areas in the same focus may demonstrate a variety of pathologic findings. The basis of the lesion in all stages is a fibrous connective tissue which occupies a smooth-walled, some-

FIG. 7.—Case 5: Roentgenograms show large area of reduced density in distal metaphysis of tibia. The shadow of an oblique fracture is visible in lateral view.

times partially loculated, cavity in the bone. The bony wall may show evidence of absorption by the connective tissue, or, in areas, there may be bone apposition. Beyond the narrow zone of hypertrophied wall the

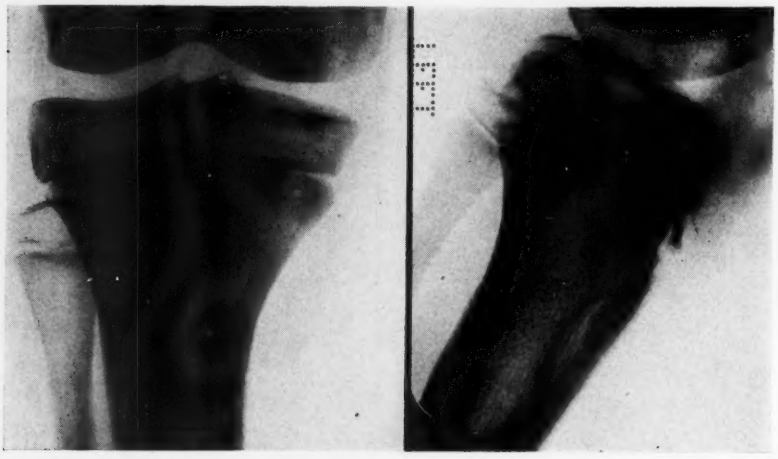


FIG. 8.—Case 6: Roentgenograms show shadow of tibial tubercle irregular in form and density. In adjacent metaphysis there is oval area of reduced density.

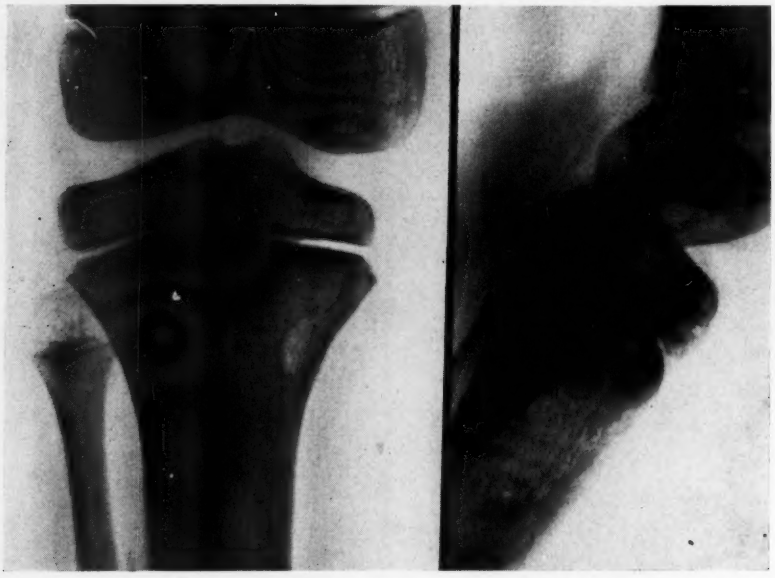


FIG. 9.—Case 7: Roentgenograms show area of reduced density in proximal metaphysis of tibia near growth disk.

marrow is normal. The recently formed focus shows a relatively cellular fibrous tissue with scattered multinucleated cells while in what appears to be a somewhat older lesion the fibrous tissue is arranged in strands and whorls. Numerous areas of recent hemorrhage and old blood pigment are seen.

Multinucleated cells may be more numerous than in the early stage. Lymphoblasts are found scattered through the fibrous tissue. Lipoid-filled macrophages are often present in focal collections or diffusely scattered through defects where roentgenographic evidence indicates a lesion of long duration. The lipoid deposition is evidence of chronicity and is not a primary feature of the disorder.

Characteristic roentgenographic and pathologic findings are illustrated in the following two cases. These sizable lesions, situated about the ankle, show bone reaction around them—indicative of relatively long existence:

Case 4.—M. G., age ten, female, had slight pain over lateral side of right ankle for three weeks. Examination revealed minimal tenderness over the distal end of fibula. Roentgenograms (Fig. 6) show an ovoid area of reduced density in the fibula 2 cm. proximal to the growth disk. This slightly expands the fibular shaft while the limits of the lesion are demarcated by a narrow shell of sclerosis. Surgical removal by curetting was done. Histologic examination shows moderately cellular fibrous tissue arranged in whorls and strands, and scattered with numerous multinucleated cells. Roentgenograms, ten weeks after the operation, showed repair of the defect.

Case 5.—L. G., male, age ten, had no symptoms referable to the left leg until he sustained a fracture of the tibia following mild trauma. Roentgenograms (Fig. 7) at this time disclosed a 2 x 2 x 4-cm. area of rarefaction in the tibia, 2 cm. from the distal epiphyseal disk. This has its longer diameter in the axis of the shaft, which it expands slightly. The irregular shadow of a narrow zone of bone sclerosis circumscribes the area and irregular trabeculation gives the appearance of multiloculation. An oblique fracture through the lesion is seen in the lateral view. Curetting resulted in complete healing. Microscopic examination shows typical fibrous tissue with moderate numbers of multinucleated cells.

THE RELATIONSHIP BETWEEN METAPHYSEAL DEFECTS AND DISTURBANCES IN EPIPHYSEAL BONE AND CARTILAGE

Disturbances of epiphyseal bone and cartilage were found in conjunction with metaphyseal defects in 14 of 45 patients. In fact, the symptoms of joint derangement led to roentgenologic examination, which disclosed the metaphyseal lesion. Osteochondritis of the tibial tubercle, Osgood-Schlatter's disease, was the most frequent associated epiphyseal disturbance being found in eight patients, who also had metaphyseal lesions. These patients complained of painful knee and had tenderness to pressure over the tibial tubercle. Their roentgenograms show irregular form and density of the epiphyseal bone of the tubercle and irregularly reduced density in the adjacent metaphyseal bone.

The following three cases demonstrate this association of metaphyseal defects with disturbance of epiphyseal bone:

Case 6.—J. R., male, age 12, had pain about the left knee for two months. There was tenderness and swelling at the tibial tubercle. Roentgenograms (Fig. 8) show irregularity in density and form in the shadow of the tibial tubercle. In addition, there is in the metaphysis of the tibia, 1 cm. distal to the tubercle, an oval area of reduced density with sclerotic margins.

In the next case excision of a metaphyseal lesion connected with Osgood-Schlatter's disease gave opportunity for histologic confirmation of its identity.

Case 7.—A. C., age ten, had pain and tenderness at the left tibial tubercle for four months. The roentgenograms (Fig. 9) show a zone of reduced density in the tibial metaphysis 1.5 cm. from the growth disk. Excision of the area was done. The histologic preparation (Fig. 10) shows fibrous tissue with multinucleated cells identical with that seen in the other cases.

FIG. 10.—Case 7: Photomicrograph shows fibrous tissue with occasional multinucleated cells.

Another case shows long persistence of the metaphyseal lesion which together with Osgood-Schlatter's disease arose from a disturbance at the growing epiphysis.

Case 8.—J. Y., male, age 13, had painful and tender tibial tubercles for two years. Roentgenograms showed irregular density and form of both tubercles and, in addition, that of the left tibia (Fig. 11a) discloses small areas of reduced density in the adjacent metaphysis. Four years later a roentgenogram (Fig. 11b) shows a rounded zone of reduced density with sclerotic margins.

Metaphyseal foci associated with Osgood-Schlatter's disease were observed in both the distal femur and proximal tibia in two patients and, in three, foci were visible in the femur but not in the tibia. The multiplicity of lesions in metaphyses found associated with an epiphyseal alteration must mean that the underlying disturbance is more extensive than has been recognized.

Osteochondritis dissecans of the femoral condyle was found in connection

FIG. 11.—Case 8: Roentgenogram A shows small areas of reduced density in proximal tibial metaphysis adjacent to tibial tubercle which is irregular in density and form. B. Four years later, shows rounded zone of reduced density with sclerotic margins.

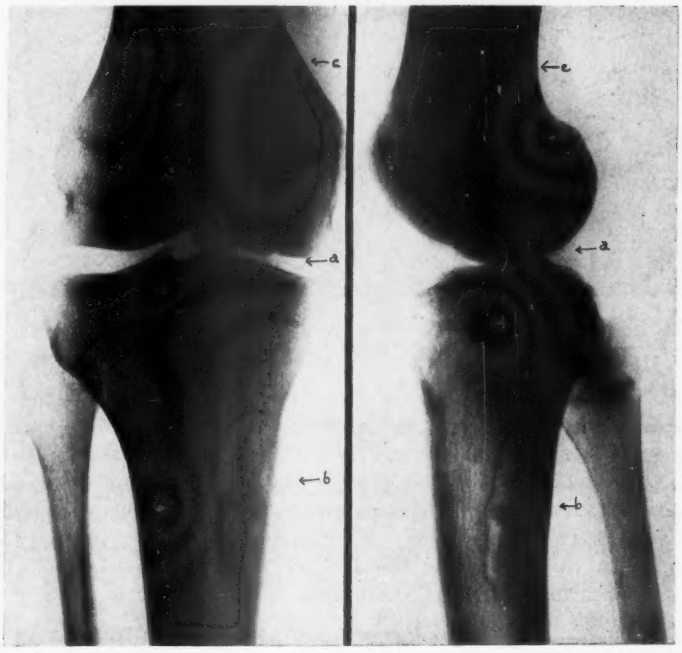


FIG. 12.—Case 9: Roentgenograms show shadow of wedge of bone of greater density separated from medial condyle (a); large area of reduced density with sclerotic margins in proximal tibia (b); the shadow of a smaller area of reduced density is visible medially in femur (c).

with metaphyseal foci in four patients. An area of demarcated rarefaction was observed in the distal femoral metaphyses in all these patients. The following patient had also a metaphyseal defect in the proximal tibia.

Case 9.—G. O., male, age 17, had, for nine years, noted intermittent aching in the left knee. For the past four months there had been attacks of painful catching of the knee in flexion. Roentgenograms (Fig. 12) disclose, in addition to the shadow of a separated wedge of articular bone in the lateral portion of the medial femoral condyle, two circumscribed areas of reduced density in the metaphyses on either side of the joint.

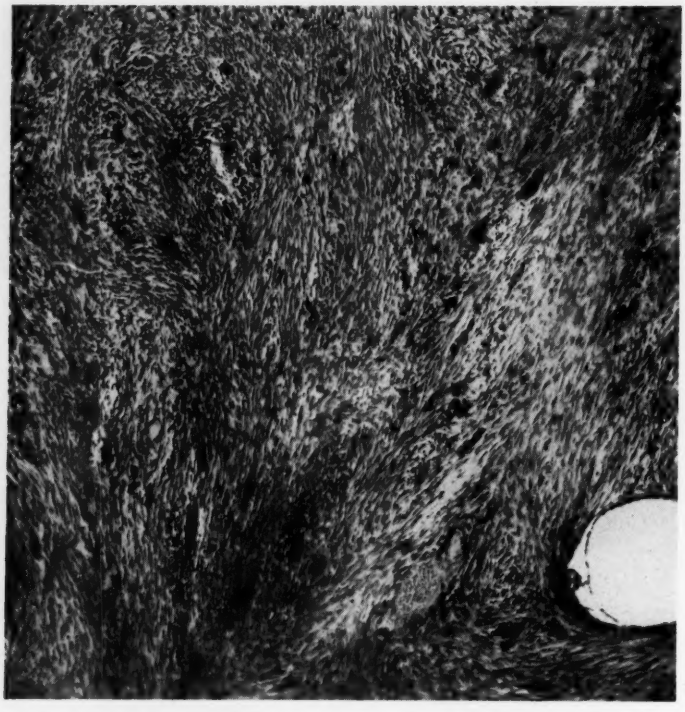


FIG. 13.—Case 9: Photomicrograph shows fibrous tissue with multinucleated cells and lipoid filled macrophages.

The one in the tibia is the larger and has more sclerosis about it. In the femoral metaphysis the area is smaller and has little evidence of surrounding bone reaction. At operation, the osteochondritic fragment was excised and the metaphyseal focus in the tibia was curetted. The material within the bone cavity was yellowish fibrous tissue. Microscopically, it consists of fibrous strands with multinucleated cells and clusters of lipoid-containing macrophages (Fig. 13). Relief of symptoms followed operation. Roentgenographic examination 18 months later shows repair of the tibial defect and healing of the undisturbed lesion in the femoral metaphysis.

Osteochondritis of the patella was present in two patients who had metaphyseal defects in the distal femoral metaphysis. Disturbance of growth from the epiphyseal cartilages about the knee, of unknown cause, was associated with a metaphyseal defect in the femoral metaphysis in one case.

THE NATURAL COURSE OF THE DISORDER—TREATMENT

It is obvious that the metaphyseal defect found commonly in childhood, and but rarely in adult life, must undergo spontaneous healing. Several modes of obliteration of the lesion have been observed. In the first place, a defect found in the metaphysis of a young child may heal rapidly by reparative ossification, or, if it is located near the margin of the metaphysis, longitudinal growth and tubulation of the bone cause it to be displaced to the outer surface of the bone and obliterated. If early repair does not occur and the lesion is so

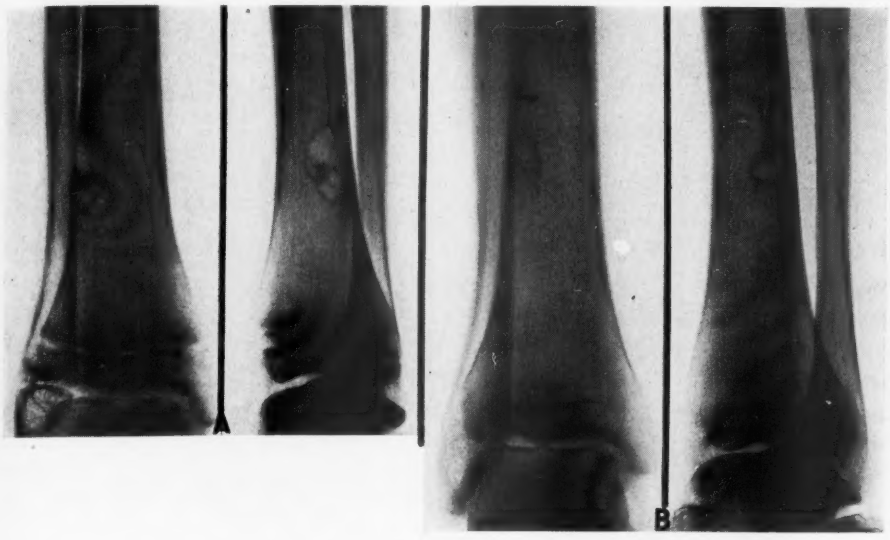


FIG. 14.—Roentgenograms show:

A. Shadow of area of reduced density with sclerotic margins.
B. Four years later, evidence of filling in by bone of normal density.

situated that it is not carried to the outer surface, it usually becomes encapsulated by a thin sclerotic wall. Such a focus may then undergo gradual obliteration by ossification from its walls. Sometimes this will result in restitution of normal architecture of the region; sometimes a localized hypertrophy of bone will remain to mark the site.

An illustration of spontaneous healing is presented in the roentgenograms (Fig. 14a) of a symptomless fibrous defect in the distal end of the tibia. During four years there was gradual filling-in of the area by normal bone to the degree noted in Figure 14b.

Occasionally the encapsulated area shows no tendency to repair and persists into adult years. Rarely may the fibrous elements of the focus continue to destroy bone and produce a gradually expanding lesion. Such was the situation in the following patient.

Case 10.—H. D., male, age 19, had noted a tender swelling over the right tibia for one month. Roentgenograms (Fig. 15) demonstrate a fairly large irregular area of reduced density with sclerotic margins. The proximal portion of this region

shows increased density, indicative of bony repair. The distal and mesial regions show little evidence of filling-in by bone. The shadow of mesial cortex bulges and is thinned over its apex. Partial ostectomy was done and the defect filled with bone chips. The histologic appearance varies somewhat in the different regions. In the more sclerotic zone the fibrous tissue is relatively less cellular and more collagenous and contains lipoid macrophage collections. Tissue from the area of rarefaction near the medial cortex is more cellular with numerous multinucleated cells and foci of lymphoblasts. The patient was relieved of symptoms by the operation, and healing resulted.

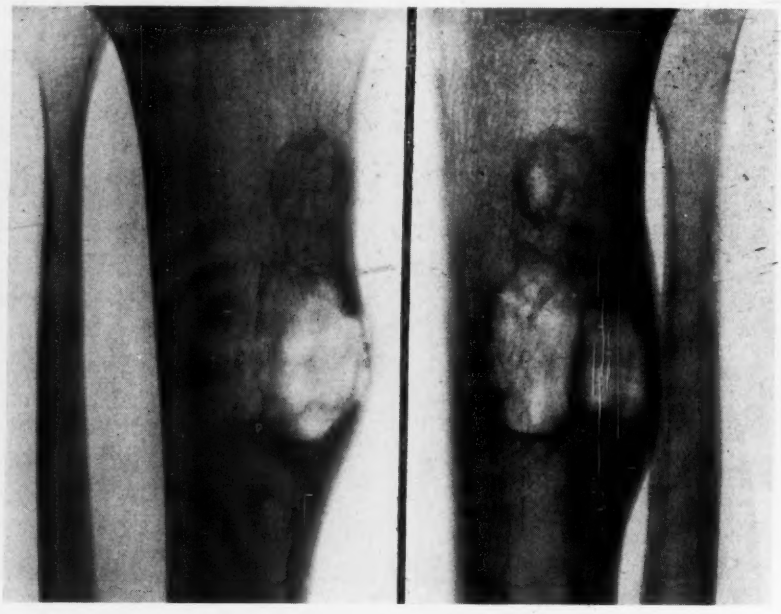


FIG. 15.—Case 10: Roentgenograms demonstrate a large area uneven in density and form in proximal portion of tibia. Proximally, there is increased density indicative of repair.

Since the lesion is usually not associated with much disability and since spontaneous repair is the rule, surgical excision is not frequently indicated. Also, the clinical and roentgenographic findings are so characteristic that confusion with solitary cysts, giant cell tumor, sarcoma, or other bone lesions requiring excision usually need not occur. In instances where eradication of the focus was indicated by persistent pain, bloc excision or curettage resulted in complete healing and no recurrences have been noted.

DISCUSSION.—Since localized fibrous lesions have their inception exclusively in childhood, and since they are always located close to the growing end of the bone, it is logical to attribute their origin to some disorder at the region of enchondral bone growth. A relation to bone growth is indicated, also, by the occurrence of the lesions in proximity to the major growth cartilages in proportion to their relative growth activity.

The association of the metaphyseal fibrous pockets with disorders of epiphyseal bone and cartilage occurs too frequently to be a mere coincidence. There is evidence that the alterations observed in the roentgenograms of the

osteochondroses do not necessarily represent the real extent of involvement. For example, in osteochondrosis of the tibial tubercle alteration of metaphyseal bone is not infrequently observed in roentgenograms; in fact, changes sufficient to produce epiphyseal separation following slight trauma have been observed.

In the cases of osteochondritis dissecans the initial epiphyseal involvement may be much more extensive than is suggested by the final separation of the necrotic fragment of bone and cartilage. Indeed, the early changes in osteochondrosis or osteochondritis are probably a local manifestation of a more general aberration in enchondral growth. Hence, Osgood-Schlatter's disorder and Legg-Perthe's disease are frequently bilateral. It is reasonable to assume that when alterations of bone occur in the secondary ossification centers, similar changes may also occur at the zone of enchondral ossification of the epiphyseal disk. The finding of metaphyseal lesions in two or more bones of the same patient seems significant in this regard.

Osteochondrosis of the capital epiphysis of the femur (Legg-Perthe's disease) is one of the most frequently observed examples of epiphyseal disorder. If the fibrous lesions have any association with such epiphyseal changes, it might be expected that they would be found commonly in the proximal portion of the femur. Such is not the case, however. It is true that some alteration of enchondral ossification at this epiphyseal disk does occur since the usual outcome is a shortened, broadened femoral neck. Juxtaepiphyseal rarefaction in the proximal femoral metaphysis may be seen in roentgenograms at certain stages of this disorder, but this usually disappears early. It is to be noted that the rate of longitudinal growth at the proximal end of the femur is slow; therefore, if a metaphyseal defect were present, it would remain close to the epiphysis and probably heal.

Except for Legg-Perthe's disease the incidence of fibrous defects in various parts of the skeleton corresponds well to the localization of epiphyseal disorders. Both are most common about the knee, that is, in the weight-bearing bones of the lower extremity. The upper extremity bones are uncommon sites for either epiphyseal or metaphyseal defects.

Objection may be raised to the assumption that all the cases described represent the same type of lesion since tissue examination was not done in each instance. However, the histologic findings in 14 cases do represent various stages of the disorder, and all show fundamentally the same pathologic characteristics. Since the clinical and roentgenologic manifestations are similar throughout the series, there seems to be no reason for not considering them all examples of the same disorder.

ETIOLOGY

The primary etiology of the metaphyseal fibrous defects is as obscure as that of the primary epiphyseal osteochondroses. In none of the cases has there been evidence of bacterial infection, or of any general disease such as neurofibromatosis, lipoid storage disease, or other defect which might have direct etiologic bearing. Jaffe and Lichtenstein hold the metaphyseal lesion

which they term nonosteogenic fibroma of bone to be a benign tumor of marrow connective tissue. The view that it is a tumor, with the usual clinical implication, is not supported by our study. While no clue as to the primary causation of the disturbance is available, the association with demonstrable epiphyseal disorder is considered significant. This association is further borne out by a similarity in course which suggests that the fibrous lesion of the metaphysis also may follow vascular derangement.

SUMMARY

1. A study of 45 patients who had metaphyseal fibrous defects in the bones of the lower extremities is reported, and pathologic findings in 17 cases are described.

2. Concomitant epiphyseal disorders were observed in 14 cases. The probable significance of this relationship is pointed out.

3. Spontaneous healing of the fibrous metaphyseal lesions was usual. In few cases was surgical eradication necessary for relief of pain.

4. There is evidence that the disturbance which results in metaphyseal and/or epiphyseal disorders is not as localized as is usually thought.

5. Although the primary etiologic factors are unknown, there is sufficient similarity to the course of recognized epiphyseal disturbances to suggest a common pathogenesis.

REFERENCES

1 Phélip, J. A.: Ostéite kystique vacuolaire juvénile xanthomateuse de l'extrémité inférieure du femur. Mém. Acad. de chir., **61**, 443–446, 1935.

2 Burman, M. S., and Sinberg, S. E.: Solitary Xanthoma (Lipoid Granulomatosis) of Bone. Arch. Surg., **37**, 1017–1032, 1938.

3 Geschickter, C. F., and Copeland, M. M.: Tumors of Bone. Am. Jour. of Cancer, New York City, 1936, rev. ed.

4 Phemister, Dallas B.: Chronic Fibrous Osteomyelitis. ANNALS OF SURGERY, **90**, 756, January, 1925.

5 Jaffe, H. L., and Lichtenstein, L.: Nonosteogenic Fibroma of Bone. Am. Jour. of Path., **18**, 205–221, 1942.

BILATERAL ADRENALECTOMY IN PROSTATIC CANCER

CLINICAL FEATURES AND URINARY EXCRETION OF 17-KETOSTEROIDS AND ESTROGEN*

CHARLES HUGGINS, M.D., AND WILLIAM WALLACE SCOTT, M.D.

CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF CHICAGO, CHICAGO, ILL

METHODS which inhibit androgenic production or action either by orchiectomy or estrogen administration have been found to reduce the activity of cancer of the prostate in many instances[1, 2]; in other cases these measures fail to control the disease, either immediately or more often following a remission of some months or years. It has been postulated that the production of androgen by organs other than the testes is responsible for the activity of prostatic cancer where control of the testicular androgens has resulted in failure, either immediate or delayed.

There is considerable evidence that the adrenal cortex of several species, including man, elaborates androgens in amounts of physiologic significance. Androgen-producing tumors occurring in the adrenal cortex, especially of women and little boys, often lead to masculinization—regression of the pathologic status occurring after extirpation of the tumor. The X-zone of Price[3] occurring in the adrenal cortex of young rats induces pubertal changes in the prostate of males castrated early in life. In guinea-pigs which had been castrated shortly after birth, tumors of the adrenal cortex developed after many months, inducing maturity in the secondary sex organs[4]; Wooley and Little[5] observed that early orchiectomy in male mice of the strain JAX ce produced adrenal tumors with masculinization in some and estrogenic effects in the accessory sex organs of others. After orchiectomy for prostatic cancer there is a fall in the urinary excretion of total neutral, as well as *beta,* 17-ketosteroids followed by a considerable increase for prolonged periods.[19] This preliminary fall appears to be dependent upon the removal of the gonads and is not an indifferent effect of the operative procedure. Further, it seems likely that the increase is induced through the adrenal cortex by way of the pituitary gland.

The study of prostatic cancer has been hampered by the rarity of this disease in laboratory animals. Adrenocarcinoma of the prostate gland has not been produced in the laboratory; the implantation of 1:2 benzpyrene in the prostate of rats[6] has resulted in the production of squamous cell carcinoma, a type which is rare in man. Prostatic cancer occasionally occurs spontaneously in the dog. Schlotthauer and Millar[7] observed it in three dogs, and Krause,[8] and Roth,[9] in single cases. Engle and Stout[10] discovered prostatic cancer in a

* This investigation was supported by grants from Mr. Ben May and Mr. T. M. Stevens, of Mobile, Alabama, and from the Committee on Research in Endocrinology, the National Research Council.

monkey at autopsy. We have observed adenocarcinoma of the prostate twice in a series of 637 dogs whose prostate glands were examined cytologically in this laboratory. The disease has never been recognized in a living laboratory animal so that functional observations have not been feasible in the lower forms.

In experimental animals the adrenal glands have been removed with preservation of life and good health for many months by means of substitution therapy. Because of the hypothesis that adrenal androgens were stimulating the growth of prostatic cancer and since the natural life expectancy clearly was short in the cases to be considered in this paper, the adrenal glands were removed in two stages from four men with rapidly growing metastatic cancer of the prostate, all having had the previous benefit of orchiectomy. These men survived 1.5, 1.5, 11 and 116 days after bilateral adrenalectomy, and are the basis of the present communication. In this paper it will be demonstrated that there is an additional factor in some prostatic cancers, namely, androgen-independence.

Since postoperative adrenal failure occasionally occurs following less drastic adrenal surgery, the methods by which survival occurs after complete adrenalectomy are presented in detail. Complete adrenalectomy in man, with survival, has not been described previously.

CASE REPORTS

Case 1.—A. E. D. (history No. 266,424), a physician, age 58, was first seen on July 9, 1941, complaining of sciatica of six months' duration. The prostate gland was hard, nodular, fixed and very large. A roentgenogram showed widespread osteoplastic metastases in the pelvis. The serum acid phosphatase was 7.5 units* and alkaline phosphatase 36 units.

A diagnosis of cancer of the prostate was made, and bilateral orchiectomy was accordingly carried out on July 17, 1941. Relief of pain occurred within six days, and shortly thereafter the patient resumed the practice of his profession. Seven months after orchiectomy, acid and alkaline phosphatase values were 4.5 and 6 units respectively. One month later a reactivation of the disease occurred, judging by a rise of alkaline phosphatase, which was progressive. In June, 1942, pain reappeared and became steadily worse, requiring injections of morphine. On January 25, 1943, the left adrenal gland was removed through a loin incision; its weight was 5.4 Gm., and it was normal on cytologic study. The blood pressure was 120/84. The serum sodium and potassium were normal. On February 12, 1943, the right adrenal was removed under ethylene anesthesia; it was normal in appearance and weighed 5.5 Gm. The blood pressure was unchanged for 12 hours when it decreased to 70/60. The temperature rose to 38.2° C. eight hours after operation, rising to 40° C. at 20 hours. The patient died in shock 36 hours after removal of the second adrenal. At no time were the values for serum sodium and potassium abnormal, and the blood sugar ranged from 82 to 131 mg. per cent.

Prior to castration the total neutral urinary 17-ketosteroids ranged from 5 to 7 mg. per 24 hours (Fig. 1). Following orchiectomy there was no immediate change in these values, but from day 13 to 20, the 17-ketosteroids fell to less than the preoperative level; however, over the course of a few months to a year and a half they gradually rose to

*All phosphatase results are expressed in King and Armstrong units per 100 cc. of serum.

12 mg. per day, almost twice the level found prior to castration. Following removal of the left adrenal gland there was a moderate decrease in 17-ketosteroid excretion; following right adrenalectomy there was a sharp reduction to a level of 2.0 mg. for the first 24 hours. Obviously, this patient did not live long enough for us to make any significant observations either clinically or chemically except that the treatment of acute adrenal insufficiency was inadequate.

Special therapy in this case included adrenal cortical extract* 35 cc. intramuscularly on day 0 minus 1† 50 cc. on 0 day; and 50 cc. on 0 plus 1. Desoxycorticosterone acetate (DCA)‡ was injected in amounts of 5 mg. on 0 day and 20 mg. on 0 plus 1. A transfusion of plasma, 600 cc. was given on 0 plus 1.

Autopsy revealed adenocarcinomas of the prostate with metastases to lymph nodes and bone.

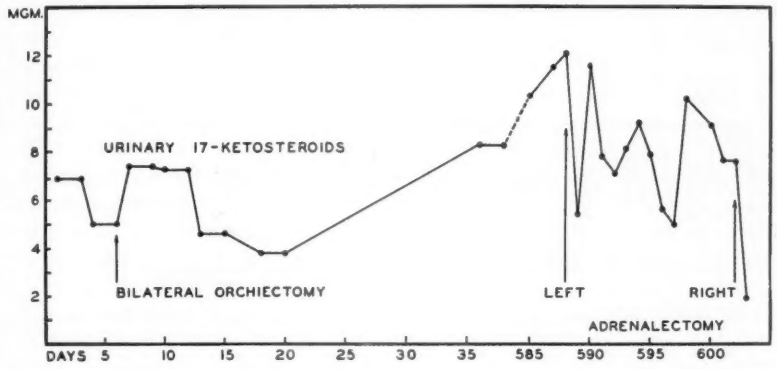


FIG. 1.—Excretion of total urinary 17-ketosteroids following orchiectomy and adrenalectomy, Case 1.

Case 2.—W. E. B. (history No. 312,344), a clerk, age 60, was first seen on June 23, 1943, complaining of pain in the lower back and in both legs for one month. For several years there had been urinary frequency. The prostate gland was large (4+), hard and nodular, and acid and alkaline phosphatase values were 3.75 and 24 units. A diagnosis of carcinoma of the prostate was made and bilateral orchiectomy performed on July 1, 1943, with complete relief of pain for five months, so that the patient resumed his work. The prostate became soft and atrophic except for slight induration in the left lobe. In December, 1943, sciatic pain recurred and became severe.

The patient was readmitted on May 7, 1944. The prostate gland was much smaller than before orchiectomy; the right lobe was atrophic and soft, the left lobe contained a hard nodule of walnut size. The blood pressure was 155/85. The left adrenal, weighing 5 Gm., was removed on May 12; the right adrenal, weighing 4.5 Gm., was excised on June 2, 1944.

Following complete adrenalectomy the temperature rose to 38.7° C. within eight hours and continued to rise (Fig. 2). Systolic blood pressure remained between 130 and 160 millimeters for 36 hours when it fell to 70 millimeters. The pulse was feeble and rapid, and the urinary output was low. The patient died in shock 54 hours after

*Adrenal cortical extract used was the 10 per cent alcoholic extract of the adrenal glands, and was prepared by the Upjohn Company and the Wilson Laboratories.

†0 minus 1 signifies the day before the operation; 0 is the day of operation, *etc.*

‡We are indebted to Dr. Erwin Schwenk of Schering Corporation for the gift of this material.

adrenalectomy. Some degree of adrenal insufficiency followed the removal of the first adrenal gland as reflected by a lowering of serum sodium to 134 m. eq. per liter and an elevation of the serum potassium to 5.6 m. eq. per liter. These values for sodium were the lowest obtained for this patient and were determined on May 29, 1944. However, by the morning of June 2, 0 day, the values for sodium and potassium were normal, 141.2 and 4.3 m. eq. per liter, respectively.

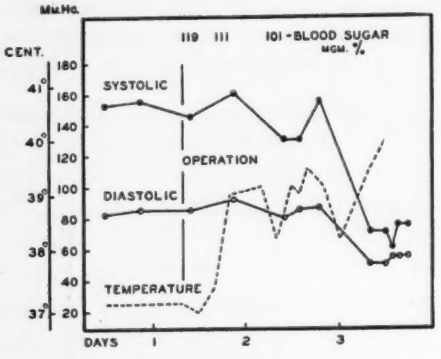


FIG. 2.—Decrease of blood pressure and increased body temperature in adrenal insufficiency of surgical type, Case 2.

Special therapy in this case included DCA, 10 mg. on days 0 minus 1, 0 day, 0 plus 1 and 0 plus 2; adrenal cortical extract 45 cc. on 0 day and 0 plus 2.

Autopsy revealed an undifferentiated carcinoma of the prostate, which appeared degenerated in many areas, with metastases to bones and lungs.

Case 3.—G. T. R. (history No. 269,817), a clerk, age 56, was first seen September 4, 1941, when he complained of urinary frequency for nine months and sciatica in the left leg for six weeks. The prostate was convex, hard and nodular, with extracapsular infiltration, but roentgenograms of the pelvis were interpreted as normal. Acid

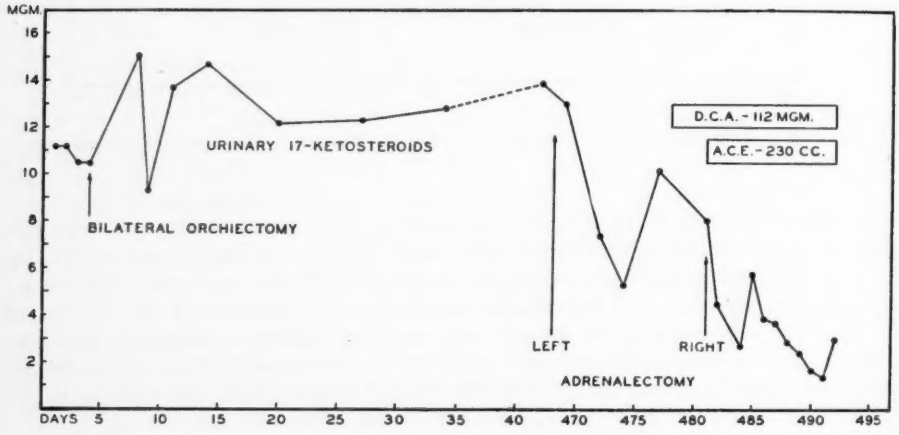


FIG. 3.—Decrease of total urinary 17-ketosteroids after adrenalectomy, Case 3.

and alkaline phosphatase values were 43 and 16 units respectively. Since the diagnosis of cancer of the prostate was certain, the testes were removed on September 16, 1941. The symptoms were improved and the patient returned to work. One year postoperatively the serum phosphatases were normal; the patient felt well and the prostate was soft, atrophic and without clinical evidence of carcinoma. One month later sciatica appeared in the right leg and rapidly became severe and required morphine and the patient was readmitted on December 22, 1942. At that time the prostate was atrophic, and the blood pressure was 134/72. Roentgenograms showed osteoplastic metastases in the pelvis. Acid and alkaline phosphatase values were 7 and 40 units. The left adrenal, weighing 5.5 Gm., was removed on December 30, 1942. The right adrenal weighed 6.5 gm. at removal on January 11, 1943. The temperature rose to 39.4° C. within four

hours thereafter and the blood pressure fell to 70/40 in 16 hours. The postoperative period was very stormy. During the early postoperative period the blood pressure and the urinary output were low; later the systolic blood pressure was increased to 150 millimeters and the daily output of urine was increased, but the patient became edematous, his fever persisted, and he died on 0 plus 11. The serum sodium and potassium were respectively 143 and 5.6 m. eq. per liter on 0 plus 8. Alkaline phosphatase values decreased from 40 to 11 units during the period of survival after complete adrenalectomy.

Preliminary total urinary 17-ketosteroids ranged from 10 to 12 mg. per 24 hours. Unlike the majority of patients we have studied these values did not undergo a preliminary decrease after orchiectomy, but rose instead, the rise being sustained for a period of 470 days (Fig. 3). After removal of the left adrenal there was a gradual fall in urinary ketosteroids; after removal of the right they continued to fall reaching their lowest value of 1.4 mg. per day on 0 plus 9 day. These values for 17-ketosteroids occurred in spite of the administration of desoxycorticosterone acetate and adrenal cortical extract. Comb-growth androgens determined before either adrenal was removed were of the order of 25 I. U. per day. Zero values were obtained on 0 plus 9 day indicating total absence of androgen excretion.

At autopsy, carcinoma of the prostate was found; there was marked regression of the primary tumor associated with very malignant metastases to bone.

Case 4.—F. A. (history No. 315,065), a blond laborer, age 45, was first seen on August 4, 1943, complaining of progressive urinary frequency and dysuria for one year. The prostate was firm, nodular and fixed. Acid and alkaline phosphatase values were 6 and 11 units, respectively, and roentgenograms showed a normal pelvis. On August 11, 1943, the testes were removed, and a biopsy of the gland through a perineal incision revealed an undifferentiated cancer of the prostate. For the next eight months the patient was relieved of his symptoms. The nodularity and induration of the prostate disappeared.

Ten months after orchiectomy the patient developed sciatica and began to lose weight, amounting to 10 kg. by the end of the 14th month. The sciatic pain became severe and morphine was prescribed. He developed edema of the thighs.

On November 11, 1944, the left adrenal gland, weighing 5 Gm., was removed, under spinal anesthesia, through a loin incision, and the right adrenal gland, weighing 5 Gm., was similarly excised on December 4, 1944. The immediate convalescence was uneventful; blood pressure was maintained at the preoperative level and there was a fever of 38° C. only on two days, 0 plus 4 and 0 plus 8. The details of pre- and postoperative treatment are given in Table I. The patient walked on the 8th day. The sciatic pain was relieved after operation but the appetite was poor. The serum sodium fell to 132 m. eq. per liter after removing the first adrenal, and at this time the serum potassium was 5.6 m. eq. per liter. There was no further reduction in serum sodium or potassium following complete adrenalectomy. Two months after the remaining adrenal was excised, the serum sodium was 140.5 and the serum potassium 5.0 m. eq. per liter.

On December 20, 1944 (0 plus 16) brown-black pigment was noted under the eyes and beneath adhesive strapping in the loin areas; the prostatic bed was soft and smooth and presented no clinical evidence of carcinoma, and the patient was discharged from the hospital. Pigmentation increased in the fingers, external genitalia and near the incisions, especially around the site of the drains, skin sutures and where adhesive tape had been located.

There followed a period of poor health featured by lack of appetite, occasional vomiting and loss of weight. On February 7, 1945, urinary retention occurred which was treated by inlying catheter. Pubic and axillary hair became sparse. A decrease of pain, estimated at 75 per cent, occurred following adrenalectomy, but opiates were still required. During the last two weeks of life there was recurrence of slight edema of the legs. The patient died 116 days after complete adrenalectomy.

The urea clearance was 45.9 cc. (85 per cent of mean normal) three weeks before death, when the patient was receiving 25 mg. of DCA daily, and phenolsulfonephthalein excretion in two hours was 85 per cent of the amount injected; blood urea was 9.3 mg. per cent. The red blood count was 4.3 millions on January 14, 1945, 3.52 millions on February 22 and 2.72 millions on March 8, 1945.

Figure 4 illustrates the urinary 17-ketosteroids during the period before and after bilateral adrenalectomy. It should be recalled that bilateral orchiectomy had been performed 15 months before these studies. In spite of no hormonal medication between

TABLE I

SUBSTITUTION THERAPY FOR TOTAL ADRENALECTOMY*

	0 minus 1 day	
D C A	5 cc. intramuscularly	10 A.M.
Adrenal cortex extract	5 cc. intramuscularly	6 P.M.
Adrenal cortex extract	5 cc. intramuscularly	10 P.M.
	0 day	
Adrenal cortex extract	10 cc. intramuscularly	6 A.M.
Adrenalectomy		8 A.M.
D C A	5 mg. intramuscularly	9 A.M.
Adrenal cortex extract	20 cc. intravenously	9 A.M.
Plasma	500 cc. intravenously	9 A.M.
Dextrose 5% in water	500 cc. intravenously	9 A.M.
Adrenal cortex extract	10 cc. intramuscularly	Each hour until 8 P.M.
Plasma	500 cc. intramuscularly	7 P.M.
Dextrose, 5% in water	500 cc. intramuscularly	7 P.M.
Adrenal cortex extract	5 cc. intramuscularly	Each hour
	0 plus 1 day	
Adrenal cortex extract	5 cc. intramuscularly	Each hour until 8 A.M.
Plasma	500 cc. intramuscularly	8 A.M.
Dextrose, 5% in water	500 cc. intramuscularly	8 A.M.
D C A	5 mg. intramuscularly	8 A.M.
Adrenal cortex extract	5 cc. intramuscularly	Every second hour until 8 P.M.
Adrenal cortex extract	5 cc. intramuscularly	Every three hours until 8 A.M.
	0 plus 2 days and 0 plus 3 days	
D C A	5 mg intramuscularly	8 A.M.
Adrenal cortex extract	5 cc. intramuscularly	Every four hours
	0 plus 4 days	
D C A	5 mg. intramuscularly	8 A.M.
Adrenal cortex extract	5 cc. intramuscularly	Every six hours
	0 plus 5 days	
D C A	5 mg. intramuscularly	8 A.M.
Adrenal cortex extract	5 cc. intramuscularly	Every eight hours
	0 plus 6 days	
D C A	5 mg. intramuscularly	8 A.M.
Adrenal cortex extract	5 cc. intramuscularly	Every twelve hours
	0 plus 7 days	
D C A	5 mg. intramuscularly	8 A.M.
Adrenal cortex extract	5 cc. intramuscularly	8 A.M.
	Succeeding days	
D C A	5 mg. intramuscularly	8 A.M.

* We are indebted to Professor George W. Thorn of Harvard University for suggesting this regimen; without his aid prolonged survival would hardly have been possible.

removal of the left and right adrenal glands these values are higher than before the removal of the left adrenal gland. This phenomenon was not observed previously. Following removal of the remaining adrenal gland, the level of urinary 17-ketosteroids, total, ketonic and *alpha* fractions, rapidly fell and remained low for 116 days, the duration of survival. These total values are higher than the actual amount of 17-ketosteroid present in that crude color as the result of impurities adds to the total color of the reaction. This is apparent from the ketonic fraction and from studies made in which the entire

urine for the last 49-day period was extracted. During this period there was excreted on average 1.0 mg. per day of ketonic 17-ketosteroid. Further purification by means of chromatographic absorption technic reduced this to less than 0.7 mg. per day. At least one crystalline substance has been isolated from this 49-day collection but as yet has not been identified.

Of interest in Case 4 was the continued excretion of estrogen in the urine after both the testes and adrenals were removed. This patient excreted about five International Units of estrogen per day, expressed in terms of *alpha* estradiol benzoate, for a period of 41 days following adrenalectomy. The source of this estrogen is speculative but may have been degradation of desoxycorticosterone acetate or adrenal cortical extract.

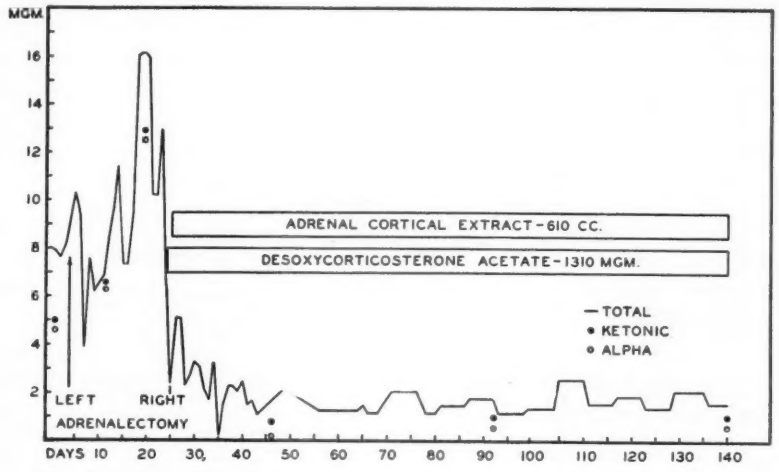


FIG. 4.—Decrease of alpha, ketonic and total urinary 17-ketosteroids following complete adrenalectomy with survival for 116 days, Case 4.

DISCUSSION.—In Cases 1 and 2 the substitution therapy was obviously inadequate since these men died 36 and 54 hours after complete adrenalectomy. The most striking effects of immediate surgical adrenal insufficiency are fever and hypotension, with death in shock; here fever of 38° to 40° C. arose within eight hours, and was maintained until death. The blood pressure remained at a normal level for 12 and 36 hours when it decreased to a shock level. The carbohydrate metabolism was not drastically affected since the level of blood glucose was not decreased and hypoglycemic convulsions were never seen. Lowering of serum sodium and elevation of serum potassium was not profound, and these levels were as much affected by removal of one adrenal as both. We are of the opinion that the large transfusions of plasma are of great aid in preserving life.

A significant effect following adrenalectomy was the rapid fall in urinary 17-ketosteroids, a fall which was persistent in the patient surviving 116 days. There has been previous, suggestive evidence that the testes and adrenals are the chief sources of the urinary 17-ketosteroids. Fraser, *et al.*,[11] giving total values of 14 and 9 mg. per 24 hours for the average excretion of 17-ketosteroids in the male and female, respectively, have postulated that 5 mg. comes from the testes and the remainder from the adrenal. Further evidence for this

concept is given by the markedly diminished or absent 17-ketosteroid excretion in the female with Addison's disease.[11, 12] Direct proof, however, such as was afforded by total absence of the testes and adrenals, has been lacking until the present study.

The rapidity of onset of pigmentation is of considerable interest. Sixteen days after complete adrenalectomy in Case 4 dark brown pigment was first observed in the lower eyelids, over the skin of the back and at the site of ad-

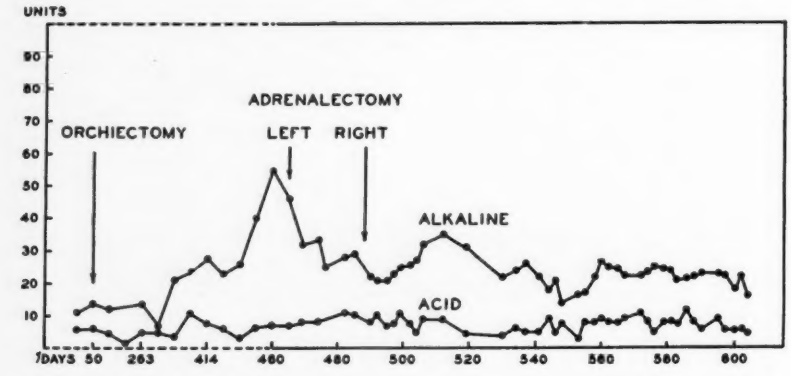


FIG. 5.—Rise in alkaline phosphatase 1 year after orchiectomy with a decrease after adrenalectomy although not to normal levels, Case 4. The phosphatase values are expressed in King and Armstrong units per 100 cubic centimeters of serum.

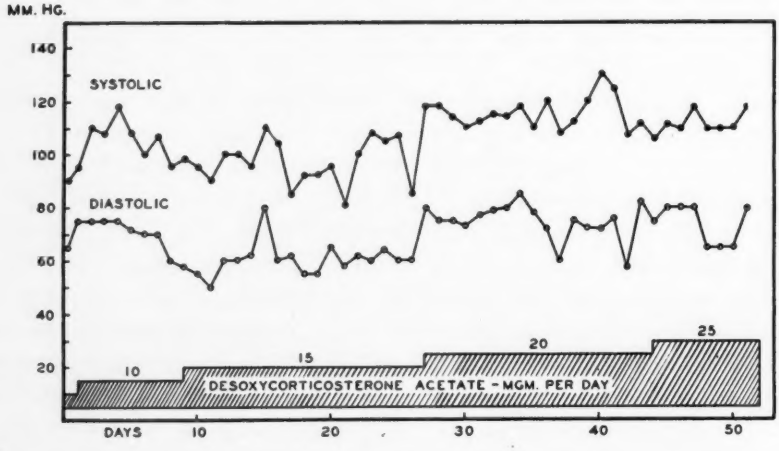


FIG. 6.—Failure to develop hypertension with increasing dosage of desoxycorticosterone acetate in an adrenalectomized man, Case 4.

hesive strapping. This coloration increased and appeared on the dorsum of the hands and on the external genitalia. The feet were uninvolved. The early appearance of this pigmentation was significant; pigmentation does not occur early in Addison's disease. The fact that the pubic and axillary hair became sparse was interesting.

The alkaline phosphatase of the serum decreased considerably after removal of both adrenals (Fig. 5) although not to normal values. This signifies a reduction in osteoplastic activity. The primary tumor also underwent a decrease in size and hardness as compared with the preadrenalectomy findings.

The effect of desoxycorticosterone acetate on blood pressure of the adrenalectomized man was of interest in that hypertension was not produced. Loeb,[13] Thorn,[14] and others,[15] have demonstrated the considerable rise in blood pressure occurring in Addison's disease as a result of overtreatment with DCA. In five of the six cases reported by McCullough and Ryan[16] hypertensive levels were reached with hormonal dosage of 10 mg. daily, or more. Clinton and Thorn[17] have found in normal subjects that a striking increase in plasma volume with retention of sodium and chloride followed the administration of 10 mg. of DCA daily.

Thorn, Koepf and Clinton[18] have described a syndrome characterized by excessive loss of salt and water resulting in collapse as a result of renal disease; these authors observed that adrenocortical homones were of no effect apparently because damage to the renal tubules rendered them unresponsive to these agents while permitting excessive loss of sodium and chloride. In Case 4 in the present paper, DCA was effective in maintaining blood pressure at normal values but hypertension was not achieved with amounts of 25 mg. daily (Fig. 6) even with addition of sodium chloride, 8 Gm. daily, to the diet; the maximum blood pressure of 130/70 was obtained with a daily DCA dosage of 20 mg. Renal damage of severe grade was eliminated from consideration in this case since phenolsulfonephthalein excretion, blood urea and urea clearance values were within the normal range. This case is, therefore, exceptional with respect to resistance to DCA, but the reason for the lack of response is not clear.

Advancing carcinomatosis in man with low androgenic activity calls for a reëxamination of the factors involved in prostatic cancer. Three factors may be discerned at the present time, namely, the testicular androgens; the extragonadal androgenic depot (which may now be stated to be the adrenal glands exclusively); and androgen-independence. In many patients widespread carcinomatosis undergoes involution, both extensive and prolonged, following excision of the testes; here clearly the tumor is androgen-dependent and the testes are producing a highly significant fraction of male hormone, In a very few cases estrogen is required after orchiectomy to control the neoplastic activity and the extragonadal depot may be postulated as a complicating androgenic factor.

The androgen-independent cancers are those in which antiandrogenic therapy fails. Following castration of normal males the prostate undergoes great reduction in size and there is a cessation of secretion; the epithelium of the normal prostate shrinks markedly in size *but the epithelial cells do not disappear.* Androgen is responsible for the development of the prostatic cells and alveoli, but having developed they acquire a value which permits survival

(in a vestigial condition) in the androgen-free state and, thus, are androgen-independent. Androgen-independence is not remarkable since it is physiologic; what is noteworthy is the necessity for many of the prostatic cancers to be furnished with androgen for their continued activity.

CONCLUSIONS

Abundant use of plasma transfusions seems to be of great importance in preventing circulatory collapse following adrenalectomy in man.

Inadequate therapy after adrenalectomy in man results in early hyperpyrexia and hypotension; the carbohydrate metabolism is not drastically disturbed. In the adrenalless man adequately treated with plasma, adrenal cortical extract and desoxycorticosterone acetate these effects were not observed but addisonian pigmentation occurred on the 16th postoperative day, and was progressive.

Complete adrenalectomy in castrate man results in a reduction of 17-ketosteroids to values less than two milligrams excreted in the urine daily; total, ketonic and *alpha* fractions are greatly diminished. Urinary androgens as measured by the comb-growth technic were absent. There is a continued excretion of small amounts of estrogen. In a man who survived complete adrenalectomy for 116 days there was a sustained reduction of alkaline phosphatase activity of the serum but the prostatic cancer progressed, although apparently at a retarded rate. DCA elevated blood pressure to normal levels but hypertension did not occur with massive doses.

The extragonadal androgenic depot in man is the adrenal.

Adrenalectomy is not a practical method of treatment of the failure-group of patients with prostatic cancer treated by antiandrogenic methods.

Three factors, whose presence and significance vary in the human prostatic cancers, may be stated: They are the testicular androgens; the extragonadal depot; and androgen-dependence or its opposite, -independence. It is not yet possible to define androgen-dependence or -independence in chemical terms.

BIBLIOGRAPHY

1 Huggins, C., and Hodges, C. V.: Cancer Research, **1**, 293, 1941.

2 Huggins, C., Stevens, R. E., and Hodges, C. V.: Arch. Surg., **43**, 209, 1941.

3 Price, D.: Am. J. Anat., **60**, 79, 1936.

4 Spiegel, A.: Virchows Arch. f. path. Anat., **305**, 367, 1939.

5 Wooley, G. W., and Little, C. C.: Cancer Research, **5**, 211, 1945.

6 Moore, R. A., and Melchionna, R. H.: Am. J. Cancer, **30**, 731, 1937.

7 Schlotthauer, C. F., and Millar, J. A. S.: J. Am. Vet. Med. Assoc., **99**, 239, 1941.

8 Krause, C.: Zeits. Path., **41**, 405, 1931.

9 Roth, L.: J. Am. Vet. Med. Assoc., **95**, 232, 1939.

10 Engle, E. T., and Stout, A. P.: Am. J. Cancer, **39**, 334, 1940.

11 Frazer, R. W., Forbes, A. P., Albright, **F.**, Sulkowitch, H., and Reifenstein, E. C., Jr.: J. Clin. Endocrinol., **1**, 234, 1941.

12 Friedgood, H. B.: The Chemistry and Physiology of Hormones. Washington, 1944. Amer. Assoc. for Advance. of Sci., p. 195.

[13] Ferrebee, J. W., Ragan, C., Atchley, D. W., and Loeb, R. F.: J. Am. Med. Assoc., **113,** 1725, 1939.
[14] Thorn, G. W., and Firor, W. M.: J. Am. Med. Assoc., **114,** 2517, 1940.
[15] Soffer, L. J., Engel, F. L., and Oppenheimer, B. S.: J. Am. Med. Assoc., **115,** 1860, 1940.
[16] McCullagh, E. P., and Ryan, E. J.: J. Am. Med. Assoc., **114,** 2530, 1940.
[17] Clinton, Jr., M., Thorn, G. W., Eisenberg, H., and Stein, K. E.: Endocrinol, **31,** 578, 1942.
[18] Thorn, G. W., Koepf, G. F., and Clinton, M.: New England J. Med., **231,** 76, 1944.
[19] Scott, W. W., and Vermeulen, C.: J. Clin. Endocrinol., **2,** 450, 1942.

SUBTOTAL REPLACEMENT OF THE SKIN OF THE FACE

FOR ACTINODERMATITIS DUE TO ROENTGENOTHERAPY: WITH MULTIPLE AREAS OF SQUAMOUS CELL CARCINOMA

HILGER PERRY JENKINS, M.D.
CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF CHICAGO SCHOOL OF MEDICINE, CHICAGO, ILL.

ALTHOUGH SKIN GRAFTS about the face are the subject of frequent reports, the replacement of all the skin of the face except for the eyelids and forehead is somewhat unusal.[1] A case is herewith presented in which skin grafts were used to replace the skin from ear to ear across the face from just below the eyes to beneath the chin and along the under side of the mandible. In addition, a nasal reconstruction was performed.

Case Report.—Mr. M. was 46 years of age when admitted to the University of Chicago Clinics and Hospital. He gave a history of having received a series of 25 roentgen ray treatments about 15 years previously. These were given for the most part over a period of four months for a pustular dermatitis of the face, which the patient described as "barber's itch." Other than evidence of a burn from the roentgen ray treatments the patient did not notice anything unusual about his face until the past two or three years during which time small weeping lesions would appear which would crust over. When the crusts were removed there would be a small ulcerated area. These would cause burning and itching. About seven months previously he noticed a lesion such as this developing on his nose. This became progressively worse.

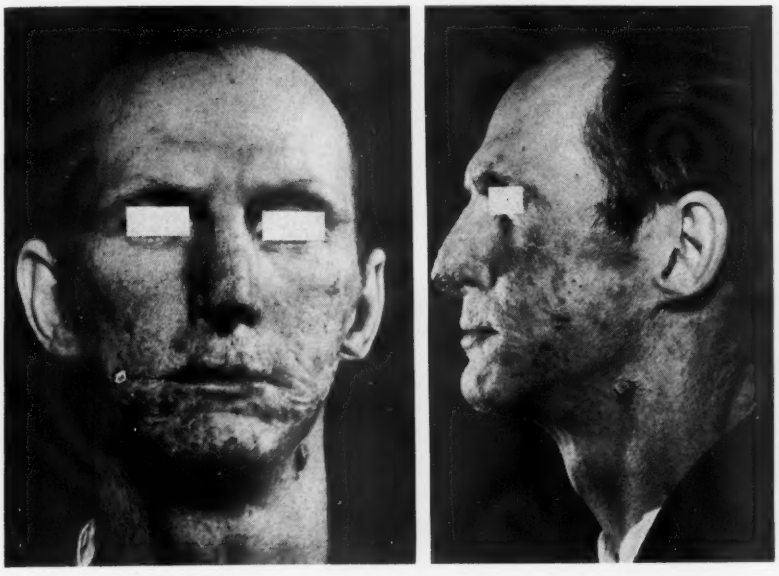
At the time of his admission his general physical examination was essentially negative except for his face and neck. There were multiple small crusted lesions about the face and especially the nose. The intervening skin was white and scarred, and drawn tightly over his features. There were several enlarged, hard firm lymph nodes on the right side of the neck (Fig. 1).

The diagnosis was made of actinodermatitis from roentgen ray, with multiple areas of squamous cell carcinoma. It was presumed that the carcinoma was the result of malignant degeneration of the roentgen ray-damaged skin. In addition, there appeared to be metastatic carcinoma in the cervical lymph nodes.

The first procedure was a radical resection of the cervical lymph nodes on the right side of the neck. The microscopic sections confirmed the diagnosis of metastatic carcinoma of the lymph nodes. Subsequently, the lesion on the nose was excised. These first two procedures were done by Doctor Brunschwig. The patient was then transferred to my service for further work. The problem which presented itself was whether one should endeavor to locally excise multiple small lesions of squamous cell carcinoma which were present in several different parts of the face or, to do nothing further, pending the results of the radical resection of the lymph nodes of the neck, or to proceed with a wide excision of all the skin of the face which had been damaged by the roentgen ray.

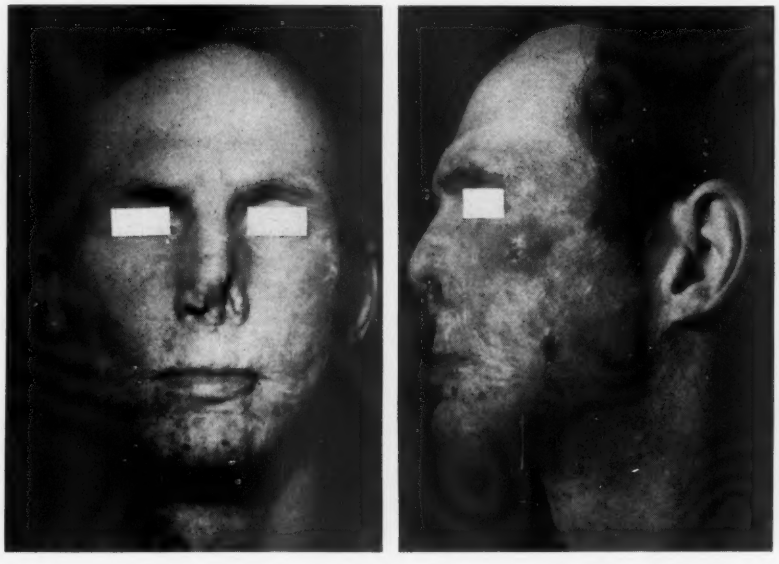
The plan of procedure which was decided upon was the wide excision of all the roentgen ray-damaged skin along with the areas which had undergone malignant degeneration and replace this with extensive dermatome skin grafts for both sides of the face and lips and a pedicle graft for the nose. This was planned, of course, in multiple stages (Fig. 2).

The pedicle graft for the nose was prepared by making parallel incisions in the skin



A B

FIG. 1.—(A—Front view): Showing actinodermatitis of face from X-ray treatments given 15 years previously. There are multiple areas of squamous cell carcinoma which have developed in past few years which involve nasal tip, chin, cheek, and neck.
FIG. 1.—(B—Side view).



A B

FIG. 2.—(A—Front view): Showing condition of nose following removal of squamous cell carcinoma of nasal tip.
FIG. 2.—(B—Side view).

of the left arm and elevating the intervening skin and subcutaneous tissue from the muscular fascia. These incisions were then sutured with fine dermal sutures and allowed to heal over. After two weeks the upper ends of the outlined pedicle was cut across, the upper portion of the pedicle elevated and the skin then sutured with fine dermal. After another three weeks the entire pedicle was elevated by cutting again through the previously healed incisions. The defect was closed by pulling the skin together over this area. There was no evidence of impairment of the blood supply, and so the remaining skin of the nose was excised and the pedicle sutured into place. The arm was held in position by a plaster of paris encasement (Fig. 3). The base of the pedicle was cut across after two weeks, and the free end of the detached pedicle on the nose was then trimmed and moulded into shape to produce the nasal tip, columella, and alae.

FIG. 3.—Showing pedicle skin graft from arm to reconstruct the nasal tip and replace the rest of the skin of the nose.

After the graft to the nose was well healed, one of the more noticeable lesions which was on the left cheek was excised and the defect closed with a relatively small free graft. This was done because this lesion, which was another area of squamous cell carcinoma, was ulcerated and infected and it did not seem advisable to include such an area in the region of a large graft. The next stage was the wide excision of the skin of the left side of the face. This was begun in front of the ear and extended across the face, under the eyes to the skin of the reconstructed nose. The skin was left on the upper and lower lip and the angle of the mouth up to a line where a crease in the skin would normally occur when smiling. The excision of skin was extended down to the under side of the mandible. The removal of the skin was carried out by sharp dissection from the underlying tissues. Constant irrigation with isotonic saline was carried out during the dissection. Bleeding points were clamped with small hemostats which were subsequently released after all the skin was removed. Persistent bleeding

points were then ligated with No. 5-0 silk. A cardboard pattern was cut to fit the defect. A dermatome skin graft was removed from the abdomen, 15/1,000 inch in thickness, and trimmed to match the cardboard pattern. The graft was sutured into place along the margins of the defect with No. 5-0 solid filament silkworm gut which was provided with a fine curved needle swedged on the suture. No fenestrations were made in the graft.

In addition, a small lesion on the side of the neck was locally excised. An emulsion ointment of sulfathiazol[2] was applied over the graft and a mechanic's waste pressure dressing applied. The dressings were not removed until two weeks after the operation, at which time the graft was found to be in relatively good condition.

A B

FIG. 4.—(A—Front view): Showing result of extensive skin grafts to face nine months after completion. The nose was reconstructed from a pedicle from the arm. The skin of the face was replaced from ear to ear and from below the eyes to beneath the mandible by dermatome skin grafts.
FIG. 4.—(B—Right side of face).

Two small ulcerated lesions, one on the chin and another on the right cheek were excised locally before proceeding with further grafting. Both of these were squamous cell carcinoma. The wounds resulting from the two small excisions healed over very slowly, and further grafting was postponed until complete healing had occurred.

The next major stage consisted of the removal of the skin of the right side of the face. This was performed in the same manner, and to the same extent, as was done on the left side of the face. The dermatome graft was taken from the back, and was 15/1,000-inch in thickness. Dressings were removed after two weeks and the graft found to be in good condition.

The final stage consisted of the removal of the remaining skin of the upper lip, lower lip, chin and angles of the mouth. The skin was removed up to the muco-cutaneous line of the lips. A dermatome graft was trimmed to a cardboard pattern of the defect and then cut transversely in the center to provide for the mouth. This part of the graft was sutured to the mucous membrane of the lips and angles of the mouth at the vermilion border. The periphery of the graft was sutured to the margins of the defect which on either side consisted of the edges of the previous grafts. Sulfathiazol ointment dressing was applied and an attempt to maintain pressure on the graft with a mechanic's waste dressing was not especially satisfactory. It was necessary to remove the dressings after six days. Several serum accumulations were evacuated with a fine needle and syringe. Most of the graft remained viable but there were several small areas of necrosis. These areas ultimately healed over without requiring further grafting.

The various stages of this subtotal replacement of the skin of the face was done under local anesthesia using 0.5 per cent novocaine.

There was some degree of scarring which remained at the junction of the graft about the mouth with the large lateral grafts, which was not entirely satisfactory from a cosmetic standpoint at the time the patient was discharged from the hospital.

The length of the hospitalization for the reconstruction procedures was nine months. Seven months after discharge, the patient returned for a check-up. At this time the grafts were soft and pliable and the junction of the major grafts was not easy to detect (Fig. 4). There was no evidence of recurrence of the squamous cell carcinoma.

C

FIG. 4.—(C—Left side of face).

The patient returned again a year later (two years after the radical resection of the metastatic carcinoma in the cervical lymph nodes). At this time, the skin grafts of his face were in excellent condition. It was very difficult to identify the junction of the major grafts. The skin was soft and pliable and moved freely with the face muscles. There was no evidence of recurrence of the carcinoma in the field which had been grafted. The reconstructed nose was in good condition. The patient had been advised to avoid direct sunlight on his face to avoid pigmentation of the grafts. At this time, the color of the grafts was, of course, lighter than the skin of his forehead. The patient had not found it necessary to use a cosmetic on the grafted area and had not been disturbed by such differential in color as was present. From the standpoint of obtaining a better color-matching in such cases, one should, of course, consider the possibility of resorting to the tattoo method, described by Hance, Brown, Byars, and McDowell.[3] Simple cosmetics, and especially "Covermark," can generally suffice in most instances.

From the standpoint of reconstruction surgery, this patient represented a very satisfactory end-result from extensive skin replacement. However, a hard nodule was found on the right side of his neck at about the level of the angle of the mandible. This was explored and found to be recurrent squamous cell carcinoma. The tumor mass was

adherent to the internal carotid artery for a distance of 3 cm. beyond the junction with the common carotid. The mass was dissected from the wall of the internal carotid without damaging the vessel. It was not deemed advisable to risk an hemiplegia by resecting the internal carotid which had been adherent to the tumor mass. A radium plaque was subsequently applied to this area in an attempt to control the growth of any tumor tissue which may have been left on the vessel wall. The patient made a satisfactory recovery from these procedures. However, the ultimate outcome is awaited with some degree of apprehension.

COMMENT: This case report is presented to illustrate what can be done in the way of extensive replacement of the skin of the face. There are numerous instances of patients who have received roentgen-ray burns of the skin of the face. Some of the more severe burns may undergo malignant degeneration of the damaged skin. If one awaits the malignant change, and the subsequent metastases to the cervical lymph nodes, the opportunity for a permanent cure is not good. The very satisfactory cosmetic result which was obtained in this case poses the question as to whether one would not be justified in undertaking such extensive removal and replacement of the skin of the face for severe roentgen-ray burns before there is definite evidence of carcinomatous change. This would constitute a prophylactic measure in the treatment of a precancerous lesion which may at some time become carcinomatous and subsequently invade the regional lymph nodes, as occurred in this case. In addition, the cosmetic result would be more acceptable than the severe roentgen-ray burn of the face. In such cases it would probably be desirable to use a free graft to replace the skin of the nose instead of a pedicle graft which was necessitated in this patient because of the removal of the nasal tip. Furthermore, there may be a wider field for the use of such large grafts to replace the skin of the face which has been severely scarred from acne alone, without the superimposed damage from roentgen ray. The smooth, soft texture of the skin graft would offer an improvement over the irregular scarred surface of the skin in very severe cases of acne. Severe thermal burns involving the entire face would probably constitute the widest field of usefulness for extensive grafts such as were employed in this case.

SUMMARY AND CONCLUSIONS

A case of severe actinodermatitis of the face from roentgen ray, associated with multiple areas of squamous cell carcinoma is presented. This was treated by extensive removal in stages of all the skin of the face except for the eyelids and forehead, and replacement by dermatome skin grafts in three major stages, and a delayed pedicle graft from the arm to the nose in four stages. The satisfactory cosmetic result which was obtained in this case, raises the question as to whether this type of procedure, with some modifications, may not be appropriate for severe roentgen ray burns of the entire face as a prophylactic measure before carcinomatous changes occur, as well as on the basis of the cosmetic improvement which may be obtained.

REFERENCES

[1] Brown, J. B., and McDowell, F.: Skin Grafting of Burns. J. B. Lippincott Co., Philadelphia, 1943.

Barsky, A. J.: Plastic Surgery. W. B. Saunders Co., Philadelphia, 1938.

Manual of Standard Practice of Plastic and Maxillofacial Surgery. W. B. Saunders Co., Philadelphia, 1942.

Sheehan, J. Eastman: A Manual of Reparative Plastic Surgery. Paul B. Hoeber, Inc., New York, 1938.

Fomon, S.: The Surgery of Injury and Plastic Repair. Williams and Wilkins Co., Baltimore, 1939.

[2] Jenkins, H. P., Allen, J. G., Owens, F. M., Schafer, P. W., and Dragstedt, L. R.: Further Studies on the Preparation and Use of Sulfathiazol Ointment in the Treatment of Burns. Surg., Gynec. & Obst., **80**, 85, 1945.

[3] Hance, G., Brown, J. B., Byars, L. T., and McDowell, F.: Color-matching of Skin Grafts and Flaps with Permanent Pigment Injection. Surg., Gynec. & Obst., **79**, 624, 1944.

CONGENITAL CATARACTS FOLLOWING RUBELLA IN PREGNANCY

ARLINGTON C. KRAUSE, M.D.

CHICAGO, ILL.

FROM THE SECTION OF OPHTHALMOLOGY, DEPARTMENT OF SURGERY, UNIVERSITY OF CHICAGO, CHICAGO, ILL.

THE IMPORTANCE of an exanthematous disease in the production of congenital cataract was first emphasized by Gregg[1] before the annual meeting of the Ophthalmological Society of Australia, in 1941. An unusual number of cases of congenital cataract scattered throughout Australia in 1941 appeared as a mild epidemic.

In 14 months, with the aid of his colleagues, Gregg collected a series of 78 cases of congenital cataracts occurring in infants. The cataracts were evident at birth, and were generally bilateral. The dense lenticular opacity was nuclear and was surrounded by a zonular haze and later by an outer clear zone. In some cases the lens was totally opaque centrally. The vision was apparently good except for the lenticular opacity. After three months searching movements occurred in the cases with bilateral cataracts because of the lack of development of fixation.

Out of 78 cases, 16 cases showed unilateral cataracts. In ten of these the eye was microphthalmic. The pupils were difficult to dilate because the infants tolerated atropine poorly. A general examination showed a congenital cardiac defect in 44 cases. At autopsy, a widely patent ductus arteriosus was discovered in three infants. In this series of cases, 15 patients died from bronchopneumonia, or unknown causes. All of the cases showed mental retardation, and most of them were feeding problems.

The frequency and geographic incidence suggested the cause was an infectious disease during pregnancy. The type of lesion led to the assumption that the disease damaged the lens during the formative period of the first few months of pregnancy. The calculation of the early months of pregnancy from the time of the birth of the child corresponded to the widespread and severe epidemic of rubella in Australia in 1940. An inquiry into the state of the health of the mother usually led either to the symptoms or to the diagnosis of German measles as the exanthematous disease during the second or third month of pregnancy. Because of the remarkable congenital defects, Gregg doubted whether the disease was true rubella.

Consequently, the National Health and Medical Research Council immediately sponsored a team of specialists to collect and correlate data of other similar cases in South Australia. Permission was requested of all medical practitioners to interview the mother and to examine the infant in all cases in which the mother had an acute exanthematous disease during pregnancy, even if the child was normal.

A series of 74 cases, covering the years 1939 to 1943, was investigated and was presented in two excellent reports[2, 3]. A definite history or diagnosis

of rubella in pregnancy was obtained in 61 mothers. Twenty infants had no evidence of the effect of rubella. The mothers of these infants had rubella

TABLE I

LIST OF ABNORMALITIES IN THE TWO SERIES OF CASES OF SWAN, ET AL., DIAGNOSED AS RUBELLA IN PREGNANCY

Unilateral cataract	1
Unilateral cataract, heart lesion	3
Bilateral cataract	5
Bilateral cataract, heart lesion	4
Bilateral cataract, heart lesion, mental deficiency	2
Bilateral buphthalmia, heart lesion, mental deficiency	1
Microcephaly	2
Microcephaly, mental deficiency	1
Heart lesion	8
Heart lesion, deaf-mutism	3
Deaf-mutism	9
Obliteration of bile ducts	1
Hypospadias	1
No abnormalities related to rubella	20

late in pregnancy. Of the 41 infants who had congenital abnormalities (see Table I), the mothers generally dated their rubella before the fourth month of pregnancy. The infant frequently had more than one organ affected. Out of the 15 patients having cataracts, 11 were bilateral and four unilateral. One patient had bilateral buphthalmia. The disease early in pregnancy from the first three weeks to the end of the third month tended to damage the eyes. Cataract was the common ocular disease. Microcephaly occurred in three infants but it was not obvious until later in the growth of some children. Mental retardation was evident in four infants. The loss of vision or hearing and the age of the child prevented the establishing of diagnosis of mental deficiency. With the handicap of loss of these senses it was difficult to estimate the mentality of the infants. Congenital deaf-mutism was present in 11 infants. The deafness was not complete but was in the low tones. Heart lesions were discovered in 21 infants. In some cases the positive clinical evidence of heart disease was not confirmable upon roentgenologic examination. The roentgenologic examination often revealed heart abnormalities not discovered clinically. The common heart lesions found at autopsy were patent ductus arteriosus, intraventricular septal defects, and patent foramen ovale. The heart was affected early in the pregnancy in the first three months. Later, Swan[5] mentioned hyalinization and sclerosis in the glomeruli of the kidney in a few patients, and Evans[6] noticed dental aplasia was a common defect. Young[4] later reported a case of deafness in an infant who had rubella at the age of four months.

Swan, *et al.*, believed that the reason for the lack of previous observations on the association of cataracts with rubella in pregnancy was related to the increase in the severity of the disease during the past few years in Australia, Great Britain and the United States. Other reports[7, 8, 9] have suggested an increase of virulence or a shift in the activity to other tissues as a cause for the severity of the disease. Some of the congenital cataracts

and other abnormalities in cases which were listed by Swan but included in the series of cases with undoubted rubella were perhaps related to mothers with mild or no symptoms of rubella.

Reese[10] reported on three cases of cataract following a severe epidemic of German measles. One infant with a congenital heart lesion had an unilateral cataract in a microphthalmic eye. In the second infant which was microcephalic there were cataracts in each microphthalmic eye. The heart lesion was diagnosed as patent intraventricular septum. The third infant had bilateral cataracts in microphthalmic eyes. The heart had a patent ductus arteriosus. No operations were performed to remove the cataracts.

Erickson[11] listed the brief data on 11 cases. Bilateral cataracts were evident in seven infants, unilateral cataracts with microphthalmia in two, unilateral microphthalmia in one, and unilateral corneal opacity with microphthalmia in one infant. Nine infants had congenital cardiac defects and two had mental retardation.

Perera[12] has recorded one case. The infant, age 4.5 months, had an unilateral congenital cataract and cardiac disease. After operation the lens was still absorbing slowly.

The total number of cases in which pregnant women were diagnosed as having rubella were 68 by Gregg (10 of 78 were discarded by Swan, *et al.*, as insufficient histories of rubella infection), 41, by Swan, *et al.*; 3, by Reese; 11, by Erickson; and 1, by Perera, or a total of 124 cases. Of the 124 cases, 96 had cataracts.

A series of rubella cases which were seen at the University of Chicago Clinics is presented here.

CASE REPORTS

Case 1.—P. B. was born in an outside hospital on October 26, 1943, during a normal delivery after eight and one-half months gestation, with a weight of 1,100 Gm. She was kept in the hospital for two and one-half months until she weighed 2,720 Gm. At the age of three weeks the infant was found to have cataracts in each eye.

The father, age 25, and brother, age two, were always healthy. The mother, age 22, in the seventh week of pregnancy had the symptoms of rubella.

In February, 1944, the child was seen in the University Clinics. A diagnosis of prematurity, congenital heart disease, congenital displacement of the fourth toes and bilateral congenital anterior uveitis and cataracts were made.

On April 18, 1944, an eye examination was made. The child avoided light. No vision of moving objects was obtained. Externally the eyes were normal. The bulbs were small. The right cornea was 6.5 mm. and the left was 7.0 mm. in diameter. No precipitates were seen on the posterior surface of the clear corneas. The anterior chambers were very shallow. The irides were muddy-gray in color and had lost most of the pigment of the posterior epithelium. The pupils were 2 mm. in diameter and fixed by posterior synechiae. The pupillary reflex was pinkish-gray centrally and red peripherally. The lenticular nuclei were diffuse opaque gray and the cortex was almost clear. The anterior surface of the capsule was lightly covered with a fine gray veil and sprinkled with melanotic pigment granules. The lenses were slightly displaced up and in. The electrocardiograph indicated no definite abnormality. The roentgenologic examination showed an indistinct congenital vascular anomaly of the heart. The dental

development was delayed. Hearing appeared to be not subnormal. In spite of the loss of vision the child was not considered to be remarkably mentally retarded by the child psychologist.

On October 24, 1944, the eyes were reëxamined. The corneas were then 8 mm. in diameter. The lenticular nuclei were denser. On October 30, 1944, a Barkan operation was performed on the right eye and a week later on the left eye. After the operations the fundi appeared normal except for the absence of the foveolar reflex. The child was given eight diopter glasses. A psychologic test showed that the child was greatly improved mentally.

This case is unusual because bilateral fetal iritis was present. The operation was successful in removing the opacity and in increasing the vision. The question of whether or not the iritis will remain quiescent and not cause obscuration of the vision cannot be answered as yet.

Case 2.—H. B., a white male, was born, April 17, 1943, in the University of Chicago Clinics after a gestation of 28 weeks. The child was not cyanosed or jaundiced. The healthy infant weighed 985 Gm. on the seventh day. The delivery was uncomplicated. The placenta was normal. No instruments were used. No cause was known for the prematurity.

The mother, a primipara, age 29, and the father, age 33, were healthy. The mother had rubella in the second month of pregnancy. Ocular, nervous and familial disease were not evident in the relatives of the parents.

The child was placed in an heated oxygen chamber. Vitamin K was given. On May 4, an upper respiratory infection caused a mild cyanosis and slight jaundice. After treatment with sulfathiazole the disease was cured. The hemoglobin dropped from 18.5 Gm. (Hayden-Hansen method) on May 2 to 8 Gm. on May 21. Intravenous blood transfusions brought the hemoglobin up to 11.5 Gm. on June 12. On October 20, the child was discharged from the hospital. The eyes appeared to be normal. The weight was 4,255 Gm.

In November, 1943, the mother noticed that the child did not see objects or light and did not pick up anything unless it was placed in his hand. Several physicians examined the child and suggested that cataracts caused the blindness.

On July 27, 1944, an examination was made. The child was normal physically. The Wassermann test of the mother was negative. The blood count, hemoglobin and urine of the child were normal. Roentgenologic examination of the skull and chest was negative. The fronto-occipital diameter of the head was 43.5 cm. The child showed, by psychometric tests, a marked mental retardation which was not related to blindness.

The eyes gave no reaction to light and turned in 15°. The external ocular movements were unrestricted. The bulbs appeared to be normal in size. The corneas were 11 mm. in diameter and were hazy posteriorly. The right anterior chamber was shallowed in the middle and absent peripherally where the iris was adherent to the cornea. The left anterior chamber was absent except inferiorly and nasally where it was extremely shallow. On the left iris, a prominent radial vessel extended to the pupil from below. Transillumination of the bulbs gave a pinkish-gray pupillary reflex. The intra-ocular tactile tension was low. The fixed pupils were irregular and adherent to the white opaque lens. The right pupil was 3 mm. in diameter and the left 2 mm.

The patient was last seen on July 29, 1944.

A diagnosis of bilateral fetal uveitis, bilateral congenital cataract, cerebral agenesis and mental retardation was made.

Case 3.—B. M. was born February 10, 1945, with a weight of 2,295 Gm. after a 28-week gestation. The mother had German measles during the second month of pregnancy. At birth, the corneas were slightly cloudy. After examination, a diagnosis of prematurity, with multiple congenital anomalies was made. The new born infant

had spina bifida with loss of function below T 12, congenital cardiac anomalies, congenital cataract of left eye. The infant died on the 30th day of life.

Uncontrollable circumstances did not permit a further examination of this and other infants.

Case 4.—J. P., born December 15, 1944, was a full term child who was seen at the age of 10 months. Two weeks before the first missing menstrual period of pregnancy the mother had German measles. The child was always mentally and physically retarded. A congenital cataract was removed from the left eye at the age of five months. The vision appeared to be fair.

An examination showed a left convergent strabismus, left postoperative aphakia, dental aplasia, bilateral total deafness, and mental and physical retardation. No cardiac abnormalities were found. The fundi seemed to be normal except for the absence of foveolar reflexes.

The interesting point in this history is the accurate-dated record of rubella two weeks after the last menstrual period.

Case 5.—R. S., born in 1942, was seen at the age of two years. The mother had German measles in the second month of pregnancy. The examination of the child revealed a loud apical and basal murmur in the chest, vision of gross objects particularly with the use of his left eye, in spite of bilateral lens opacities, fair hearing and a low mentality based on psychometric tests. A diagnosis of bilateral congenital cataracts, congenital heart disease, cerebral agenesis and mental retardation was made.

DISCUSSION.—Married women who know that rubella may give rise to congential defects in children have asked about the possibility of becoming infected with rubella during early pregnancy. If the women are in contact with the migratory people from camps and cities they have a much better chance of infection than women who are relatively isolated. Husbands on leave from the Armed Forces may spread the disease to their wives. If the women had rubella in the past, the chances of having another attack of the disease are very remote. One mother in the Australian series of cases asserted that she had a previous attack of rubella. There are other rare instances in which a second attack has occurred.

Nonmedical persons have regarded rubella as a mild disease which needs little or no treatment. According to two Australian reports, about half of the 41 mothers with affected infants received medical counsel when they had the disease. The question arises whether or not the public, particularly married women, should be informed of the dangers of infection with rubella. If they are exposed to rubella in early pregnancy, treatment with convalesecent serum should be considered. Perhaps it might be well to require that the disease, especially in married women of child-bearing age, be reportable to local or state public health service. Since these infants with serious congenital defects may have mental retardation, loss of sight and hearing and generally poor health, they are incapable of taking care of themselves. They represent a social problem.

Treatment should be considered in women with a questionable pregnancy or a pregnancy of the first three months with a history of rubella. The ratio of infants with congenital defects to those with no defects in mothers with rubella is too high to be disregarded. The only possible but presumptive

method of treatment seems to be the use of convalescent German measles serum.

Whether or not rubella can affect the fetus if the woman has the disease just before pregnancy is questionable. Gregg[1] reported one woman who had rubella three months before pregnancy but the infant had congenital rubella cataracts. There is no doubt that viruses may persist in the tissues but the persistence of the German measles virus is unknown. There seems to be little reason at present to give treatment before pregnancy or after six known months of pregnancy.

Perhaps induction of the disease before pregnancy may be a means of preventing the possibility of occurrence of the disease during pregnancy in those who are exposed to it.

A therapeutic abortion may be considered if the disease has occurred in the first four months of pregnancy.

The surgical treatment of these cases with congenital defects varies with the organ involved in the disease. The cataract should be treated surgically as soon as possible in the first few months of life, before the development of fixation. Time of operation makes a great difference in bilateral cataract. The type of operation will vary with the surgeon and his experience. The hard central lenticular nucleus should be removed. It usually takes a long time, sometimes months, before a clear pupil is formed after an operation. The absorption of lens substance, according to the experience of those who have operated on the rubella cataracts, is delayed. An operation at three months of age is late because by the time the pupil is clear the ability to develop fixation may be lost. The ophthalmologist usually sees these infants after the pediatrician or physician has treated the child for malnutrition. A common belief is held that these infants are too young for operative procedures on the eye. A better procedure would be to have the obstetrician consult the ophthalmologist as soon as the infant is found to have white pupils, poor sight, or as soon as the pregnant woman with a history of an exanthematous disease in the first four months of pregnancy is first seen by him.

All children with congenital cataracts related to rubella should have their hearing tested for range. Low tone deafness may be missed in ordinary tests. According to the report of Swan, *et al.*, hearing aids have been tried satisfactorily on a few infants. Deafness and deaf-mutism are added factors contributing to mental retardation.

The patent ductus arteriosus is a common defect in these infants, and is usually contributory to their poor health. A successful surgical procedure to correct this condition has been developed. In one case[3] this operation resulted in a distinct improvement of physical condition of the child.

SUMMARY

The literature on effect of rubella in pregnancy is reviewed. A report on five cases with congenital anomalies including cataract is given. Preventative, conservative and radical treatment of fetal rubella is discussed.

REFERENCES

1 Gregg, N. M.: Congenital Cataract Following German Measles in the Mother. Trans. Ophth. Soc., Australia, **3**, 35, 1941.

2 Swan, C., Tostevin, A. L., Moore, B., Mayo, H., and Black, G. H. B.: Congenital Defects in Infants Following Infectious Disease during Pregnancy: With Special Reference to the Relationship between German Measles and Cataract, Deaf-mutism, Heart Disease and Microcephaly, and to the Period of Pregnancy in which the Occurrence of Rubella is Followed by Congenital Abnormalities. Med. Jour. Australia, **30**, (2), 201, 1943.

3 Swan, C., Tostevin, A. L., Mayo, H., and Black, G. H. B.: Further Observations on Congenital Defects in Infants following Infectious Disease during Pregnancy: With Special Reference to Rubella. Med. Jour. Australia, **31**, (1), 409, 1944.

4 Young, J. H.: Rubella and Congenital Deaf-mutism. Med. Jour. Australia, **30**, (2), 451, 1943.

5 Swan, C.: Congenital Defects in Infants following Infectious Diseases. Med. Jour. Australia, **30**, (2), 411, 1943.

6 Evans, M. W.: Congenital Dental Defects in Infants Subsequent to Maternal Rubella during Pregnancy. Med. Jour. Australia, **31**, (2), 226, 1944.

7 Evans, F. B. P.: Severe Rubella. Brit. Med. Jour., **1**, 240, 1942.

8 Sprott, N. A.: Is the Virus of Rubella becoming Neurotropic? Brit. Med. Jour., **2**, 154, 1940.

9 Humphrey, T. F., and Ekermeyer, E. W.: Rubella: Report of Epidemic with Unusual Number of Complications and Relapses. Ohio State Med. Jour., **33**, 406, 1937.

10 Reese, A. B.: Congenital Cataract and Other Anomalies following German Measles in the Mother. Amer. Jour. Ophth., **27**, 483, 1944.

11 Erickson, C. A.: Rubella Early in Pregnancy Causing Congenital Malformations of Eyes and Heart. J. Pediatrics, **25**, 281, 1944.

12 Perera, C. A.: Congenital Cataract following Rubella in the Mother. Amer. Jour. Ophth., **28**, 186, 1945.

HEADACHE FROM LESIONS OF SCALP NERVES

FREDERICK E. KREDEL, M.D.
CHARLESTON, S. C.

FROM THE DEPARTMENT OF SURGERY, MEDICAL COLLEGE OF SOUTH CAROLINA AND THE ROPER HOSPITAL, CHARLESTON, S. C.

THE CAUSE of chronic localized headache is frequently a difficult diagnostic problem. In many instances there is apparently no intracranial disorder and the origin of the pain is entirely extracranial. Disturbances within the orbit and accessory nasal sinuses are commonly associated with the symptom of headache. The following observations are recorded to illustrate the fact that some cases of localized headache arise from lesions of nerves of the scalp. The discomfort may not be of a type that is commonly associated with peripheral nerve lesions. The sharp, shooting, lancinating and radiating character of the pain, usually termed neuralgic, may not be present and the complaint is simply that of headache.

SCARS

Direct involvement of nerves to the scalp by scar tissue may cause headache without ready recognition of the relation of the scarring to the symptoms. In some instances a healed deep laceration in the region of the pain may be obvious. In others, the laceration may have been forgotten and not readily detected when examined through the covering of scalp hair. In still others, the history of closed contusion or previous infection producing scarring may not be elicited. Examples of these are cited:

ILLUSTRATIVE CASE REPORTS

Case 1.—*Case of known laceration:* W. W., a Negro male, age 25, fell from the upper deck of a ship and incurred a deep lacerated wound of the right frontal region and a linear fracture of the left occiput. One month later, he attempted to return to work but remained disabled by reason of right-sided headache and some dizziness. Examination two and one-half months after injury revealed a markedly tender spot at the superior pole of the scar. Pressure on this spot, in addition to causing pain locally and radiating over the distribution of the supra-orbital nerve, reproduced his so-called headache. The symptoms continued and the patient discovered that wearing a hat or especially a shipworker's helmet aggravated the headache. Seven months after injury the painful area of the scar was excised. Histologic study showed nerve trunks of moderate size entering hyperplastic keloidal scar tissue with distortion and compression of these nerve trunks by fibrosis. The symptoms were relieved and have not recurred nine months postoperatively.

Case 2.—*Case with unrecognized scars:* T. O., a white male, age 26, with a moderate degree of cerebral spastic paralysis, complained of headache all his life, but of increasing severity the past year. The headache was most severe in the left occipital region. Dural denervation in the region of the left middle meningeal vessels gave little relief. At the time of this operation several small scars from old lacerations were noted on the shaved scalp in the left parieto-occipital region. These were definitely tender and later infiltrations with procaine relieved the headache for short periods up

to a week. The scars were excised together with division of the greater occipital nerve at the lambdoidal ridge. Sections of the scars showed small nerve bundles distorted by both intraneural and perineural fibrosis. While the localization of the headaches to the area operated upon has been abolished, intermittent occipital headaches are still present six months after excision of the scars, in addition to numerous other vague complaints.

Case 3.—*Case of headache after contusion:* E. E. R., age 23, was struck above the left eyebrow by a blunt object and was unconscious for three minutes. Intermittent left frontal headache followed and disabled him from work. On examination three months after injury, the left supra-orbital nerve was found to be markedly tender. Pressure over the nerve reproduced his headache. The nerve was injected at its exit from the skull with 95 per cent alcohol. In spite of a satisfactory analgesia to pin-prick, the headache, while ameliorated, has persisted to some extent and there is still some apparent tenderness over the nerve, three weeks after injection. Evaluation of the findings is difficult in the face of an obvious compensation neurosis.

Case 4.—*Case of headache associated with old infection:* C. F. R., age 28, white, male, complained of migraine for about 15 years. The attacks had gradually increased in severity and frequency, occurring in recent months as often as every five days. There had been also numerous episodes of furunculosis of the neck since adolescence. There was diffuse deep scarring in the posterior occipital region and definite tenderness over the region of the greater occipital nerve on the left, the side of the migraine. Branches of the nerve together with a block of scarred subcutaneous tissue were excised at the point of maximum tenderness. There were no headaches for nine months following this procedure, after which some recurrence of unilateral headaches every two to three months ensued. These are not as severe as preoperatively and are not increasing in frequency, three years after the excision.

TUMOR

The following case is one in which a tumor apparently was the cause of unilateral headache:

Case 5.—Mrs. C. F. C., age 33, complained of migraine for many years. Her attacks of headache occurred as often as once or twice a month, were always on the right, and radiated anteriorly from the occipital region. Nausea occurred occasionally. For two years she had noticed a flat swelling over the lower occiput on the right. This was soft, movable and tender only on firm pressure. At operation, a flat fibrolipoma, 4 x 3 x 1.5 cm., was found enveloping the greater occipital nerve below the lambdoidal ridge. It was excised. Sections showed a fibrolipoma with nerve bundles compressed in the dense fibrous trabeculations. The migraine headaches ceased for five months but then recurred and have continued to the present time, 26 months postoperatively. They are much less frequent than before but of considerable severity. The area of operation is again tender. It is likely that nerve regeneration into the scar has occurred.

"NEURALGIAS"

Many patients complaining of localized headache show tenderness over a nerve to the scalp without demonstrable pathologic explanation. Results of local treatment in such cases is notoriously variable. Occasionally, one or more subcutaneous injections of procaine or other anesthetic agent produce a prolonged amelioration. Ammonium sulfate injections, as advocated by Bates and Judovich, have been of benefit in some cases particularly in the region of the greater occipital nerve. Alcohol block has been useful for the

supra-orbital nerve, since the injection may be placed with reasonable accuracy in or about the nerve at its exit from the skull. Section with excision of a segment of the nerve is indicated for intractable cases. Routine pathologic studies in a number of these have shown no lesions in the nerve. Not infrequently the headache soon appears in a new location or after some months recurs in the same area, presumably as a result of nerve regeneration. Plugging the foramen with a wisp of cotton and bone wax at the time of nerve excision seems to limit regeneration of the supra-orbital nerve.

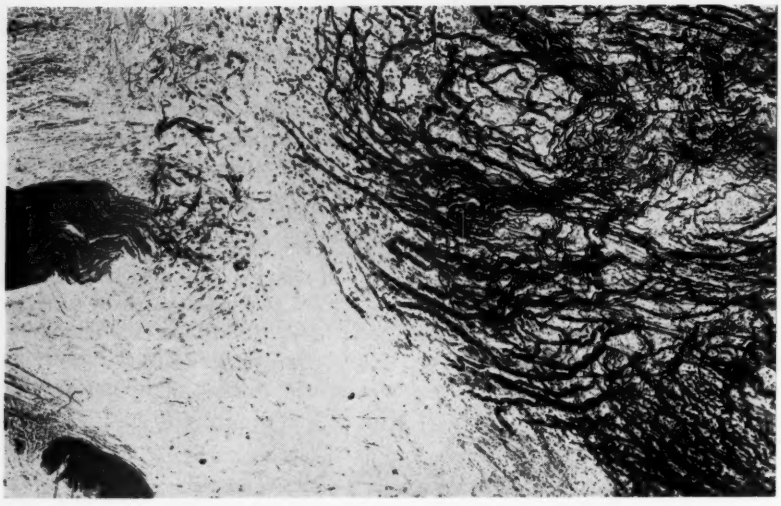


FIG. 1.—Cutaneous regeneration neuroma from a pedicled skin flap in a rabbit. Gros method × 60. From studies carried out during the author's residency under Dr. Phemister.

NERVE REGENERATION

It has been recognized that even very small nerves after division manifest a tendency to regenerate. Thus recovery of sensation occurs in both free skin grafts and pedicted flaps.[1] Kredel and Phemister observed some recovery also of sympathetic function in skin transplants. When such small regenerating nerve fibers become involved in scar tissue, cicatricial compression or microscopic neuromas occur and may lead to persistently painful scars.[2, 3] Figure 1 is a silver impregnation of a profuse neuromatous overgrowth after division of a small cutaneous nerve trunk in the rabbit.

Numerous methods have been devised in the attempt to prevent neuromas after division of larger nerve trunks. None of these are completely successful in all instances. For small cutaneous nerves, frequently not identified grossly at operation, no method of limiting undesirable nerve regeneration has been advanced. When the nerves can be seen during dissection, crushing with an hemostat proximal to a ligature of nonabsorbable material is indicated.

Simple excision of a scarred area containing a microscopic neuroma followed by primary healing does not often lead to a recurrence.[3] However,

subcutaneous nerve trunks the size of the supra-orbital and greater occipital nerves and their main branches are likely to regenerate. An effort should be made to find and treat the proximal stumps when these nerves are divided.

CONCLUSIONS

1. Some cases of localized headaches seem to originate in nerves supplying the scalp area.

2. When a definite lesion affecting the nerve is present, local surgical treatment is likely to be of benefit.

3. Injection or section of nerves without demonstrable lesions gives variable results.

4. Regeneration of divided scalp nerves may lead to recurrence of headaches.

REFERENCES

[1] Kredel, F. E., and Evans, J. P.: Recovery of Sensation in Denervated Pedicle and Free Skin Transplants. Arch. Neurol. and Psychiat., **29**, 1203, 1933.

[2] Kredel, F. E.: Painful Scars. J. South Carolina M. A., **35**, 299, 1939.

[3] Kredel, F. E.: Painful Scars. Surgery, **8**, 98, 1940.

OSTEOMYELITIS OF THE PETROUS PYRAMID OF THE TEMPORAL BONE

J. R. LINDSAY, M.D.

CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY (DIVISION OF OTOLARYNGOLOGY), UNIVERSITY OF CHICAGO, CHICAGO, ILL.

SUPPURATION of the petrous pyramid was a frequent intermediary stage in the development of complications of middle ear infection in the years preceding sulfonamide and penicillin therapy. The nature of the process and the reason for its occurrence and persistence despite mastoid surgery promoted much investigation and the basis for clinical interpretation and surgical treatment was gradually established.

While chemotherapy has provided a valuable aid in the prevention and control of such infections and greatly reduced the necessity for surgical intervention its effectiveness has been subject to certain limitations. Experience has shown these drugs to be most effective in the invasive and early stages of middle ear infection. The presence of bone involvement such as breakdown of cell partitions, osteomyelitis, and sequestration tends to limit their effect to one of localization, while a cure is still dependent upon surgical drainage.

The anatomic arrangement of the temporal bone is such that osteomyelitis and sequestration are with only rare exceptions confined to the petrous portion. Because of its close relationship to important structures complications tend to develop early. Under conditions of partial drainage the suppuration may become chronic or with inhibition of the infection by chemotherapy it may appear to subside only to become active and invade the inner ear or meninges at a later date.

The pathogenesis of the process in the pyramid formerly provoked much debate. Suppuration of the mastoid was recognized to depend on pneumatization. Gross examination of the pathologic pyramid, however, seldom permitted the recognition of pneumatic spaces and suppuration of that area was usually thought to be purely an osteomyelitis. The relation of such an osteomyelitis to infection in air cells became apparent only when the temporal bones had been removed at autopsy, sectioned serially, and studied under the microscope. Such studies of pathologic as well as normal bones have shown that the behavior of the infection within the temporal bone is primarily dependent upon the anatomic arrangement. The variation in extent and course of the disease which had been difficult to explain proved to be dependent upon variations in extent of the air cell system.

ANATOMIC CHARACTERISTICS

The petrous pyramid consists of an apical and a labyrinthine part. The apex lies medial to the labyrinthine capsule and the bony canal of the internal carotid artery and articulates with the basi-occiput and body

of the sphenoid bone. It contains marrow spaces filled in infancy with red marrow which later changes to the gray or fatty type.

The labyrinthine part of the pyramid lies between the apex and the air cell system of the middle ear and the mastoid. Marrow spaces are also present in this part in infancy and may persist throughout life. With the process of growth the pyramid enlarges by addition of periosteal bone to its surfaces. Marrow spaces expand into this new bone. As the layer of periosteal bone is thickened it becomes exposed to the forces exerted within the air cell system which produce pneumatization.

The tendency to pneumatize varies, depending probably on two factors: the amount of periosteal bone which is added to the pyramid; and the presence of normal eustachian tube function to provide free aeration.

The extent of the air cell system is of primary importance in the dissemination of infection. Petrous pyramids may be divided into two main groups: those without, and those with pneumatization. In the former group, which includes about two-thirds of adult bones, the system of air cells is limited to the mastoid with possible extensions into the zygomatic root and squama. In these, the labyrinthine capsule and the bony canal of the internal carotid artery form a natural barrier of dense bone between the marrow-containing apex of the pyramid and the air-containing middle ear and mastoid. In this group the contact between marrow spaces of the pyramid and the cell system is limited to small areas in front of or behind the superior semicircular canal. Invasion of these areas by infection does not occur; partly because their limited extent favors an adequate defense reaction, and also because the adjacent air cells drain freely to the middle ear (Fig. 1). The efficiency of this barrier is hereby illustrated in a case of middle ear suppuration in the presence of uncontrolled diabetes mellitus. In this case the reduced general resistance to infection undoubtedly predisposed to the relatively rare complication of osteomyelitis of the cranial vault as a direct extension from the mastoid cells. The marrow spaces of the apex were sufficiently protected, however, although small extensions lay adjacent to the cell system (Fig. 1) and showed an inflammatory response.

The mastoid air cells begin to form before birth and pneumatization keeps pace with growth of the bone[1]. Infection of the mastoid is, therefore, an infection of the air cell system rather than an osteomyelitis from infancy onward. Extension from the cell system to the marrow spaces of the squama or zygomatic root are rare, because erosion of the thin outer or inner cortex provides an easier exit for the suppurative process. Extension to the marrow spaces of the pyramid tends to be prevented in the infant by the labyrinthine capsule, but this natural barrier persists throughout life only in nonpneumatized pyramids.

Although invasion of the marrow spaces of the bones of the vault rarely occurs from the cell system, the reverse process takes place readily. A spreading osteomyelitis of the cranial vault easily invades the cell

system of the mastoid (Fig. 2) producing a diffuse suppuration of all middle ear air spaces. The extension of an osteomyelitis of the vault to the petrous pyramid is prevented by the interposed air cell system and the dense labyrinthine capsule. In those bones with pneumatization extending into the pyramid the comparative isolation of the apex from a middle ear infection no longer exists.

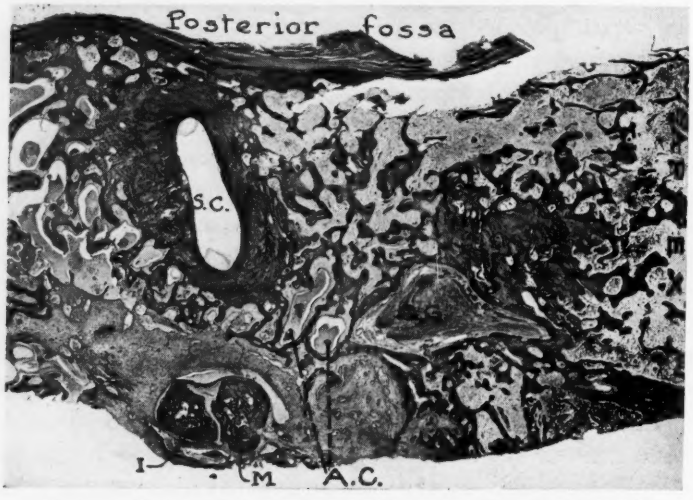


FIG. 1.—Case No. 1: Suppurative otitis media in uncontrolled diabetes mellitus in an adult. Direct extension to marrow spaces of the bones of the vault but not to the petrous pyramid.

Horizontal section through an upper level of the pyramid showing superior semicircular canal (S.C.), the geniculate ganglion (G.G.), the malleus (M) and incus (I). The air cells (A.C.) filled with exudate mark the beginning of pneumatization of the perilabyrinthine area. The inflammatory reaction and early fibrous tissue proliferation in adjacent marrow spaces has protected the apex from invasion.

PNEUMATIZATION

Extension of the cell system into the pyramid begins shortly after infancy and may be well developed by the fourth year[2, 3, 4]. It was found in one-third of all bones of four years of age and over on examination of serial microscopic sections[5].

Since the periosteal layer of bone in which pneumatization occurs varies in its amount and location, and may occur mainly on either of the inferior, posterior or superior aspects, the cell tracts which develop vary correspondingly in their location. The most frequent site of pneumatization is the posterosuperior angle of the pyramid, medial to the superior semicircular canal where a large block of bone is deposited to fill out the subarcuate fossa after birth. This area is pneumatized from the epitympanum and mastoid. Air cells beneath the labyrinth develop either from the mastoid or hypotympanum[5].

Relatively few marrow spaces may remain back of the labyrinth, but the air cells in that area may border freely on marrow spaces extending

from the apex. These perilabyrinthine air cells may be demonstrated roentgenographically on the Stenver's and occipital projections[5].

The apex of the pyramid is pneumatized to some extent in over 20

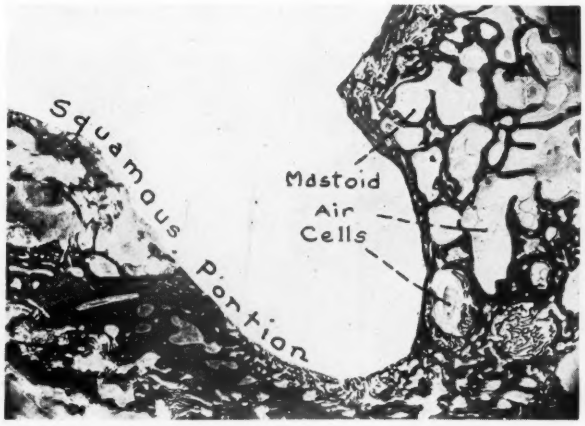


FIG. 2.—Case No. 2: Diffuse spreading osteomyelitis of the cranial vault. The section shows the extension of the osteomyelitic process in the squamous portion of the temporal bone to the air cell system of the ear.

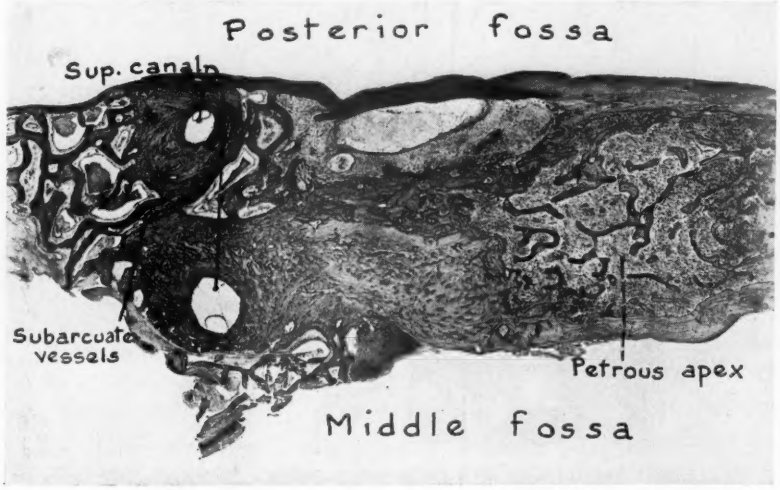


FIG. 3.—Horizontal section through the upper level of a petrous pyramid with a localized area of suppuration in the group of cells behind and above the labyrinth which extended through the cortex to the meninges. The marrow spaces of the apex show diffuse fibrosis and sclerosis. (Case reported in Ann. Otol. Rhin. & Laryng. 47: 3, 1938)

per cent of bones. The amount of marrow replaced by air cells varies, but is usually less than half. Only a single large cell may be present. This is in contrast to the apex of the monkey, where extensive pneumatization is the rule.

From a practical viewpoint a single cell may be as important as a

group of cells, since it provides a portal of entry for infection. The length and size of the channel or bottleneck through which pneumatization has developed has a greater influence on the course of the suppuration than the size of the pneumatized area.

The apex is pneumatized in two principal regions. In one group the

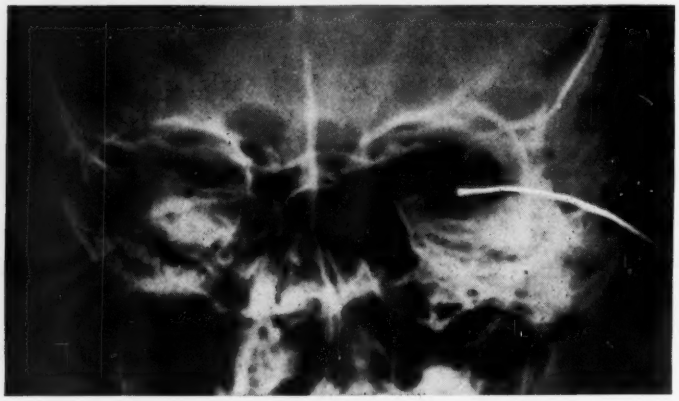


FIG. 4.—Roentgenogram of the skull in the transorbital projection made immediately after surgical drainage of the petrous apex. The end of the probe lies in the center of the suppurative focus. The apex was drained over three months after mastoidectomy. Recovery was rapid.

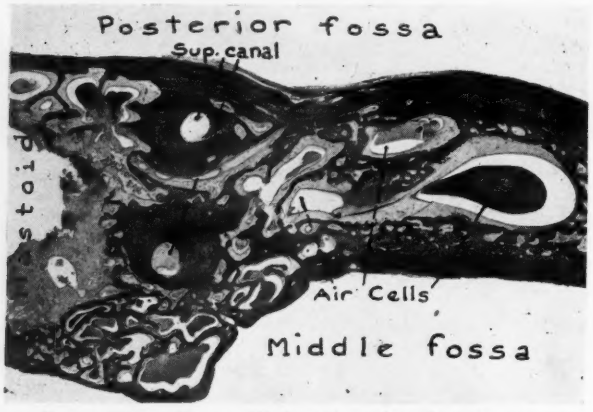


FIG. 5.—Case No. 3: Horizontal section through an upper level of the petrous pyramid showing the mastoid antrum, the superior semicircular canal, and the air cells in the apex filled with exudate. These air cells developed from the epitympanum and provided an entrance for infection. From them it extended to surrounding marrow spaces (See Figure 6) which at this level show chronic fibrosis and sclerosis.

air cells extend along the posterosuperior angle over the internal auditory meatus. This represents simply an extension of perilabyrinthine pneumatization and the cells lie in the upper half of the apex underneath the cortex of the middle fossa (Fig. 5). In the other group the cells have developed

from the tympanic cavity or peritubal cells in relation to the carotid artery, and lie mainly in the lower half of the apex.

The cells in the upper part of the apex are shown roentgenographically on the Stenver's and transorbital projections, while those in the lower half require an axial or mentovertical view.

The pathway of pneumatization provides the key to the interpretation of clinical and roentenologic findings and to the simplest route for surgical drainage.

ACUTE OSTEOMYELITIS

Invasion of the marrow spaces by infection may occur by several routes, but in the overwhelming majority it is a direct extension from the air cell system.

Hematogenous infection has occurred in severe puerperal infection and also from an osteomyelitis elsewhere in the body[6]. Such an osteomyelitis tends to spread to the air cell system.

Direct invasion of the apex from an osteomyelitis of the sphenoidal bone may occur[7] as well as the reverse process. Acute osteomyelitis has been observed also as part of a panotitis of meningitic origin in the late stages of meningitis.

Hematogenous invasion of the apex by tuberculous infection is common, particularly during a miliary dissemination,[8] and tends to involve the air cell system as well.

The common type of osteomyelitis of the pyramid is that in which the infection extends directly from the middle ear cell system along pneumatized tracts. Although the gross appearance has suggested invasion of the apex in nonpneumatized pyramids, the microscopic studies so far have consistently shown the presence of tracts of air cells leading in to the pyramid which permitted free entrance of the infection. The disease, therefore, appears to be a potential only in pneumatized pyramids.

The usual anatomic arrangement of such cell tracts is that the air cells broaden out as the tract reaches certain areas, notably the apex (Fig. 5) and the area in the angle behind the labyrinth. Since such air cells have no cilia to aid in their protection, but depend upon the circulation for mobilization of their defense, infection passes inward readily, but the resultant swelling of the mucoperiosteal lining membranes impedes drainage at the narrow points of exit. One and sometimes two bottlenecks must, therefore, be traversed by the purulent discharge in reaching the middle ear and external canal, thereby creating a tendency to obstruction of drainage.

The existence of adequate drainage has been a primary factor in the control of such infection. With the use of sulfonamides and penicillin in the invasive or early stages, such infections may now be controlled almost without exception; but after suppuration has become advanced, these drugs are less effective and adequate drainage continues to be essential for

recovery. Retention of suppuration within a pneumatized area leads to absorption and breakdown of the cell partitions with invasion of contiguous structures, the infection following the path of least resistance.

Suppuration in the group of cells behind and above the labyrinth with inadequate drainage tends to invade the middle or posterior cranial fossae. It may also cause erosion of the labyrinthine capsule and labyrinthitis. Sequestration of portions of the semicircular canals may occur in such cases[9], probably as a result of destruction of blood supply of their narrow bony walls. Chronic suppuration frequently occurs, sometimes with a persistent postauricular fistula after mastoidectomy. The occurrence of osteomyelitis appears to depend on the proximity of the marrow spaces of the apex. In some there is little involvement and in others

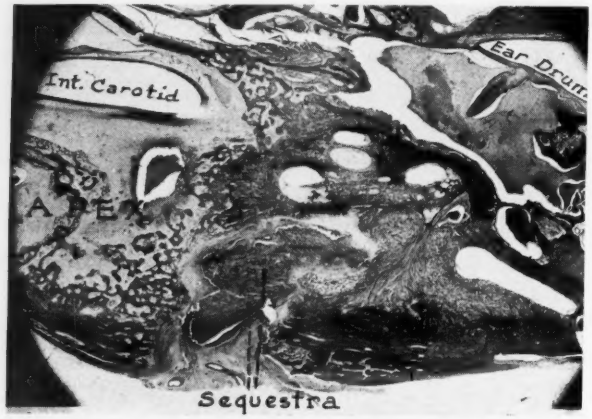


FIG. 6.—Case No. 3: Horizontal section through the midportion of the labyrinth, below the air cells shown in the apex in Figure 5.
Diffuse suppuration and necrosis involves the whole apex with several bony sequestra. The disease was localized by sulfadiazine therapy and remained quiescent for over a year but eventually destroyed the inner ear and invaded the meninges.

a localized invasion of adjacent marrow varying from a mild fibrosis to suppuration and necrosis. The tendency to produce diffuse osteomyelitis increases with the extent of the cell tract into the apex. The marrow possesses considerable capacity for resistence to infection and in some cases the cortex and meninges may be invaded while the marrow exhibits only a diffuse reactive fibrosis and sclerosis (Fig. 3). In others, irregular areas of necrosis develop and eventually the whole apex may be involved (Fig. 6). Such a suppurative focus constitutes a combination of broken-down air cells and marrow spaces. The suppuration shows a greater tendency to break through the bony cortex and invade the cranial cavity, the inner ear, or the neck than to extend as an osteomyelitis to the basi-occiput and sphenoid. Such a tendency may be due in part to the type of organism, which is usually an *hemolytic Streptococcus* or *Pneumococcus,* and seldom a *Staphylococcus.*

From a clinical viewpoint, the localizing tendency is of practical importance. The establishment of drainage during this stage is usually sufficient to effect a rapid cure. Suppuration which has been present as long as two and three months with extensive destruction of the apex may heal rapidly after surgical drainage (Fig. 4). Extension to the marrow spaces of the occiput and sphenoid may occur, however, and is indicated by clouding of the sphenoid sinus on roentgenologic examination, due either to thickening of its mucosa or suppuration. The osteomyelitis may spread to the opposite temporal bone and usually results in invasion of the meninges.

CHRONIC OSTEOMYELITIS

Suppuration in the perilabyrinthine part of the pyramid has frequently become chronic when not drained adequately, and frequently accounts for a persistent fistula after mastoidectomy and sometimes sequestration of parts of bony canals; but may not constitute an osteomyelitis. Suppuration of the apex may also become chronic and persist for years without complication. Localization of the source of discharge along with roentgenographic evidence of sclerosis may permit the diagnosis. Such suppuration is probably similar to that which occurs in the mastoid, involving air cells primarily with a reactive sclerosis of adjoining marrow spaces.

Since the development of sulfonamide therapy, a number of cases of chronic osteomyelitis of the apex have appeared which without these drugs would probably have succumbed in the acute stage to a complication. With chemotherapy the suppurative process has been localized. The course and fate of such a suppurative process varies and is influenced by such factors as the extent of the osteomyelitis and the degree of drainage. Sulfonamides in high concentration as well as penicillin therapy have sometimes failed to effect more than a temporary alleviation of the process.

This temporary localizing effect was demonstrated by the case illustrated in Figures 5 and 6. In this case the infection in the middle ear spaces due to the *hemolytic Streptococcus* gained access to the apex from the epitympanum along a pneumatized tract (Fig. 5), setting up a diffuse osteomyelitic process. The blood stream and inner ear were invaded. A thorough course of sulfadiazine together with mastoid exenteration was followed by an apparent cure and complete cessation of discharge. Fifteen months later, however, a fatal meningitis developed and on postmortem examination a chronic osteomyelitis of the apex was found with several large bony sequestra (Fig. 6).

In retrospect, it appears that the osteomyelitis was already established before the treatment was instituted. The recognition and successful surgical removal of the sequestra would scarcely have been possible, but simple surgical drainage of the apex along with chemotherapy might have obviated further complications.

An illustration of the combined effect of surgery and chemotherapy

in chronic osteomyelitis of the apex is afforded by the case illustrated in Figures 7 and 8, in which the disease has now been under observation and treatment for seven years. As in the previous case, the disease began as a unilateral middle ear infection due to the *hemolytic Streptococcus.* Invasion of the apex along a pneumatized tract was followed by cell breakdown and osteomyelitis. The inner ear was destroyed, the blood stream invaded, and an abscess formed in the neck. Following mastoid drainage and sulfanilamide therapy the acute symptoms subsided, leaving a chronic discharge from the middle ear and a fistula in the neck. The petrous apex was not drained surgically until one year later when meningitic signs appeared. Since that time osteomyelitis has spread by way of the basi-occiput and sphenoid to the opposite temporal bone, invading the middle ear air spaces and the labyrinth. Both petrous apices have been drained

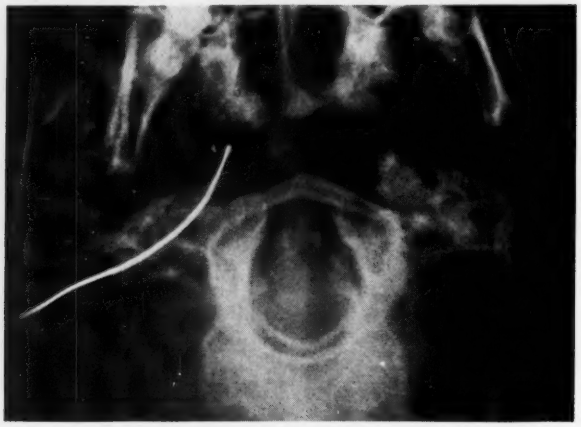


FIG. 7.—Case No. 4: Chronic osteomyelitis of both petrous apices and the body of the sphenoid, seven years duration. Roentgenogram of the base of the skull in the axial or mento-vertical projection. In this case the progress of osteomyelitis could be traced from one petrous apex across the basi-occiput and sphenoid to the opposite temporal bone. Both apices have been drained surgically. This roentgenogram shows a silver probe in one apex at operation. Defects in the bone are visible in both apices and the body of the sphenoid.

surgically along with an extremely heavy course of sulfadiazine and later penicillin. This patient continues to have an active osteomyelitis (Fig. 7) and slight discharge from both ears and the neck fistula (Fig. 8), but is otherwise in apparent good health except for total deafness.

The survival of this patient must be credited to the combination of chemotherapy and surgery. Unfortunately, at the time each inner ear was invaded, the patient was not seen in time to permit surgical drainage of the apex before function had been destroyed.

Cases such as these two illustrate clearly the limitations of chemotherapy in the present form after an osteomyelitis has once been established. Surgical drainage must be considered as an essential part of the treatment in both the acute and chronic stages, if complications such as destruction

of the inner ear or invasion of the cranial cavity are to be avoided. In the presence of chronic osteomyelitis with possible sequestration or extension to other bones of the base of the skull, a combination of chemotherapy and surgical drainage may serve to keep the process localized but fail to effect a complete cure.

SUMMARY

1. The middle ear air spaces separate the marrow spaces of the bones of the vault from the petrous pyramid and other bones of the base of the skull.

2. Infection passes readily from marrow spaces to air cells, but extension in the reverse direction meets greater resistance. The cell system, therefore, tends to limit the spread of osteomyelitis between the vault and the base of the skull.

3. Osteomyelitis of the petrous pyramid sometimes occurs by the hematogenous route or by extension from other bones of the skull base, but is usually a direct extension from middle ear suppuration.

4. The dense labyrinthine capsule forms a barrier between the marrow-containing apex and the middle ear cell system in the majority of bones. In about 20 per cent of bones, however, the air cell system invades the apex, creating a direct entrance for infection and the possibility of osteomyelitis.

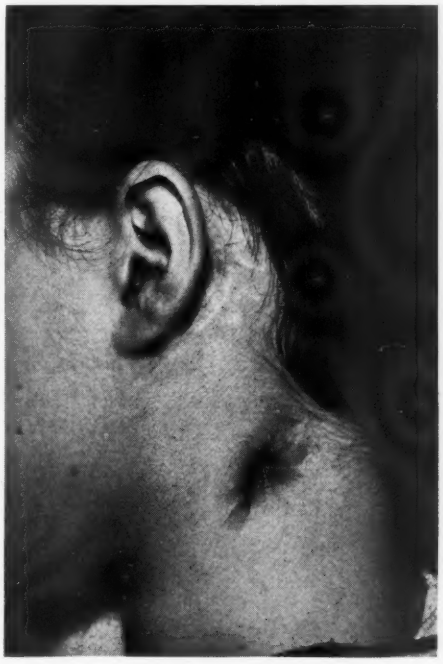


FIG. 8.—Case No. 4: Photograph showing the location of the fistula in the neck posterior to the sternocleidomastoid muscle. Purulent discharge with *hemolytic streptococcus* on culture persists from the fistula and from both ears.

5. A tendency to obstruction of drainage created by natural bottleneck predisposes to breakdown of cell partitions and invasion of surrounding marrow spaces in the apex.

6. Osteomyelitis tends to remain localized within the apex during the acute stages and responds well to surgical drainage.

7. Chemotherapy provides a valuable aid in localization, but cannot be depended upon to cure without surgical drainage.

8. In the presence of sequestration or extension of the osteomyelitis to other bones of the base of the skull, the combination of chemotherapy and surgical drainage offers a means of avoiding dangerous complications but may fail to eradicate the disease.

REFERENCES

1 Bast, T. H., and Forester, H. B.: Origin and Distribution of Air Cells in the Temporal Bone. Arch. Otolaryng., **30**, 183–205, August, 1939.

2 Guild, S. R.: Normal and Pathological Anatomy of the Petrous Pyramid. Tr. Am. Otol. Soc., **25**, 165–192, 1935.

3 Mayer, Otto: Die Pyramidenzelleneiterungen. Zeitsch. fur. Hals-Nasen und Ohrenheilk, Bd. 42, Heft 1.

4 Wilson, J. Gordon, Gaardsmoe, John P., and Anson, Barry J.: The Air Cells of the Petrous Portion of the Temporal Bone. J. Laryng. and Otol., **52**, No. 11, 746.

5 Lindsay, J. R.: Petrous Pyramid of Temporal Bone. Arch. Otolaryng., **31**, 231-255. February, 1940.

6 Wilson, J. Gordon: The Petrous Pyramid: Its Pathology. Ann. Otol., Rhin., and Laryng., **44**, 1048, December, 1935.

7 Eagleton, Wells P.: Result of Disease of the Petrous Apex and the Sphenoid Basis. Surg., Gynec., and Obst., **60**, 566–587, February, 1935.

8 Proctor, Bruce, and Lindsay, J. R.: Tuberculosis of the Ear. Arch. Otolaryng. **35**, 221–249, February, 1942.

9 Proctor, Bruce, and Lindsay, J. R.: Sequestration of the Osseous Labyrinth. Arch Otolaryng., **37**, 819–830, June, 1943.

THE PRESENT STATUS OF ETHYLENE-OXYGEN ANESTHESIA

H. M. LIVINGSTONE, M.D.

CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF CHICAGO, CHICAGO, ILL.

IT IS FITTING that a review of the present status of ethylene be made at this time. From the introduction of this anesthetic agent in humans in 1923, through 22 years of extensive clinical usage, Doctor Phemister has had intimate contact with ethylene.

In 1779, Priestley[1] referred to Ingenhousz as the first to generate ethylene. Likewise, in a Latin text (*Physica subterannea*) Becker is credited with first generating ethylene. The medical literature contains erroneous and confusing reports in regard to further investigations concerning ethylene during the next century.[2] In 1885, Luessem used an ethylene-oxygen mixture to produce unconsciousness in frogs, rabbits, a canary, two dogs and a guinea-pig, and then inhaled the gas himself, but not to the stage of unconsciousness.

Apparently, from 1885 to 1918, the only further investigations were in 1901, when Neljubow noted the effect of ethylene on etiolated seedlings, and, in 1908, when Crocker and Knight, of the Hull Botanical Laboratories of the University of Chicago, found that ethylene put carnations "to sleep."

In 1918, Luckhardt and Thompson,[3] working independently, and without knowledge of the work of Luessem and earlier investigators, established on frogs, rats and a dog both the anesthetizing and analgesic properties of a mixture of 80 per cent ethylene and 20 per cent oxygen. A report made by Brown,[4] in March, 1923, from work on mice, rabbits, cats and dogs, confirmed the results obtained by Luckhardt and Thompson.

At this time Luckhardt and Carter were establishing on themselves and others the analgesic and anesthetic properties of ethylene. On January 21, 1923, this agent was first demonstrated to a group of scientists at the University of Chicago.[3] J. B. Carter was the first human anesthetized with this gas. Doctor Phemister was the first surgeon to be anesthetized with ethylene, which event occurred on February 4, 1923. Surgical procedures under ethylene began on March 14, 1923, when Dr. Arthur Dean Bevan removed sebaceous tumors of the scalp from a patient at Presbyterian Hospital, Chicago. Dr. Isabella C. Herb was the anesthetist.[5] On April 27, 1923, Luckhardt and Carter reported the first 106 operations performed under ethylene at Presbyterian Hospital.[6]

Throughout the era of modern anesthesia, news of most new anesthetic agents spread rapidly, and soon thereafter many individuals have given these agents clinical trial. Although the next few years marked widespread use of ethylene, unfortunate newspaper publicity associated with a few explosions led to the discontinuation of its use in certain localities. Later developments have shown that the explosion potentiality of this agent is practically no

greater than that with nearly all of our inhalation agents, as will be discussed subsequently. With this additional fundamental physical knowledge, ethylene has continued to be popular in some localities, as is illustrated by such reports as 61,924 administrations at the Mayo Clinic[7]; and 35,500 at the Sayre Clinic.[8] That this agent has also aroused interest and use in foreign countries is evident from communications from Italy,[9] South America,[10–13] and Belgium,[14] among others.

It is the purpose of this communication to review the present physical, physiologic and pharmacologic knowledge of ethylene, and to evaluate clinical results with this agent.

Chemically, ethylene may be considered as dehydrated ethyl alcohol. C_2H_5OH plus heated H_3PO_4 equals C_2H_4 plus H_2O. Orthophosphoric acid was used as a decomposing agent when ethylene was first prepared by Luckhardt and Carter. Sulfuric acid has been used to dehydrate the alcohol. It may also be prepared by cracking propane. Ethylene is an unsaturated hydrocarbon gas, and adds halogen and acids. Compressed in steel cylinders, U.S.P. requirements are that a cylinder must contain not less than 99 per cent by volume of ethylene. Actually, some of the commercial products average 99.70 per cent pure ethylene (99.50 per cent minimum to 99.90 per cent). Impurities may be other hydrocarbons, such as propane, methane, or acetylene; carbon dioxide, nitrogen, hydrogen sulfide, aldehydes, phosphine, or traces of carbon monoxide. It is free from these impurities when marketed for anesthesia.

Physically, ethylene is a colorless gas with a sweet, musty odor which patients rarely find offensive. The odor varies according to the impurities in the gas. When properly made by the dehydration of alcohol it has a pleasant odor.[15] It is a nonirritating gas. Ethylene has a molecular weight of 28; specific gravity of 0.97; boils at −103° C. and liquefies at 10° C. under 60 atmospheres. It has a flash point below 32° F.

That the fire and explosion hazard is inherent in all inhalation anesthetic agents except nitrous oxide, and chloroform is well illustrated by Table I.

TABLE I

LIMITS OF FLAMMABILITY OF ANESTHETIC GASES

Substance	Atmosphere	Flammability Limits Per Cent by Volume		Sp. Gr. (Air)
		Lower	Upper	
Ether*	Air	1.85	25.9	2.56
Ether†	Oxygen	2.1	82.0	
Ethyl chloride†	Air	4.0	14.8	2.23
Ethylene*	Air	3.05	28.6	0.97
Ethylene*	Oxygen	3.10	79.9	
Cyclopropane*	Air	2.45	10.45	1.45
Cyclopropane*	Oxygen	2.48	60.00	
Vinyl ether†	Oxygen	1.8	85.0	
Acetylene	Air	3.40	52.5	
Acetylene	Oxygen	3.40	90.0	

* U. S. Bureau of Mines.

† Buchman and Wardell-Ohio Chemical Co. and Prof. Hoyt C. Hottel, Dept. of Chemical Engineering, Massachusetts Institute of Technology.

As emphasized in Table I, the fire and explosion hazard is markedly increased when oxygen is added to the anesthetic agent. Ethylene-oxygen in anesthetic mixtures usually can be administered in a range outside the flammable limits. This is not true of all inhalation agents, as can be seen in Table I.

Anyone employing ethylene should abide by the Report of the Committee on Anesthetic Accidents[16] and not use mixtures too rich in oxygen, since they stated that when the percentage of ethylene mixed with oxygen is about 25, with a considerable range above and below this percentage, the explosions are of detonating force. With still higher concentrations of ethylene in oxygen the force of the explosion decreases. At an upper limit of 80 per cent ethylene mixed with 20 per cent oxygen, explosibility ceases. Fortunately, this is a good anesthetic mixture and provides adequate oxygenation for most patients.

That the common practice of adding ether to nitrous oxide-oxygen makes a mixture which from a practical standpoint is equally dangerous, has been illustrated by explosions and deaths.[17] Greene,[18] in a clinical investigation of 230 cases of fires or explosions during anesthesia, stated that ether-oxygen, with or without nitrous oxide, has the same tendency toward propagating a wave of flame or pressure through the respiratory tract, as have ethylene-oxygen or cyclopropane-oxygen when compared under similar clinical circumstances, *i.e.,* the location of the point of ignition with reference to the respiratory tract of the patient.

Since explosions are statistically today one of the least of the hazards of anesthesia, they should not deter us from the use of any of these valuable agents, but instead only emphasize the need for the medical profession to have knowledge of anesthetic combustion, and act accordingly during the employment of these agents, to ensure their safe usage.

Among widely accepted practices that should be followed in the use of all explosive anesthetic agents are methods to eliminate static sparks, which are responsible for the greatest number of explosions. These include:

a. Wetting the mask, tubing, hands and breathing bag (if possible) immediately before the mask is applied.

b. Do not have the gas flowing at the time the mask is applied or lifted.

c. Keep the anesthetist's hand in contact with the patient's face and mask at all times when the gas is flowing.

d. No cautery or sparking device should be employed.

e. Maintenance of a relative humidity of 60 per cent, or above, in all operating rooms.

f. The Horton intercoupler or some other method of adequately grounding patient, operating table and anesthetist seems advisable.

PHYSIOLOGIC AND PHARMACOLOGIC EFFECTS

Induction of anesthesia with ethylene-oxygen is rapid and pleasant. An excitement stage seldom occurs.[2] There is no increase in mucus secretions

and no irritation of the pulmonary endothelium.[19] Respirations may be increased or slightly irregular during induction, but are normal during first and second plane of surgical anesthesia.

Spectroscopic examination revealed that apparently ethylene does not enter into chemical combination with the hemoglobin of the blood.[3] It is believed to exist in the blood in a state of physical solution, which may explain the rapid recovery period. The solubility of ethylene in blood varies with its water and lipoid content.[20] Nicloux and Yovanovitch[21] found that 70 to 80 per cent of the ethylene present in whole blood is in the cellular elements and the remainder in the plasma. They could detect only traces of ethylene in the arterial blood two minutes after administration was discontinued. Perhaps their analytic methods may not have been very sensitive. Seevers, DeFazio and Evans,[22] from analysis of intraperitoneal and subcutaneous gas pockets in rabbits, and dogs, concluded that both ethylene and cyclopropane were present in tissues many hours after the animal had apparently recovered from anesthesia. Nitrous oxide diffused through the human skin 20 times as rapidly as ethylene.[23]

Ethylene had little effect on the osmotic resistance and fragility of red cells to hypotonic saline, while ether or chloroform caused a marked reduction in the osmotic resistance of the red cells.[24]

The color of the blood should always be kept normal, and no evidence of anoxia be permitted. As with any of our anesthetic agents, the range of anesthesia for man varies considerably with the individual. That ethylene-oxygen can give second plane surgical anesthesia in many individuals without producing anoxia has been previously reported.[25] Our knowledge of the effects of specific concentrations of ethylene-oxygen is based upon arterial blood oxygen determinations made simultaneously with intratracheal, and breathing bag analyses, compared with the gas machine readings.

Relaxation with ethylene-oxygen is only moderate. It is usually adequate for everything except intra-abdominal work. It must be remembered that further decrease in the amount of oxygen in the anesthetic mixture gives lessened muscular relaxation because of the introduction of the mechanism of asphyxia. This asphyxia is manifested early in the eye. During first plane surgical anesthesia the lid reflex is rapidly obliterated but the activity of the eyeball muscles is present and a lateral oscillation is noted. In second plane surgical anesthesia the eyeball remains in the centric position indicating that the extra-ocular muscles are paralyzed and flaccid. This is aided by adequate premedication. In acute asphyxia the eyeball assumes an extremely eccentric and fixed position, either upward, or downward, or lateral. The pupil also dilates, the amount of dilatation depending upon the amount and kind of premedication used. This is due to the paralyzing effect of anoxia upon the iris muscle as well as other muscles. These manifestations are not due to the anesthetic agent *per se,* but to the asphyxia. Cyanosis is usually present with these manifestations of asphyxia, unless severe anemia or jaundice is present.

Death with ethylene is due to asphyxia. In dogs the respiratory center fails first. Heart action at the same time is quite normal and if artificial respiration is started at once the animal will recover promptly.[2] These same manifestations have been observed in humans.

During induction of anesthesia with ethylene there is no spasm due to direct irritation. According to Guedel,[26] the relative frequency of the occurrence of such spasm is seen with other inhalation agents, in the following order: ether, chloroform, ethyl chloride, divinyl oxide and cyclopropane. There is no tendency to increased laryngeal, bronchiolar, cardio-aortic or vagovagal reflexes, or any effect on cardiac automaticity as is observed in certain patients under cyclopropane anesthesia.[27] Reflex laryngospasm may occasionally be initiated by the stimulation of sensitive regions, such as periosteum, peritoneum or direct trauma to nerve trunks. It is of rare occurrence in orthopedic surgery. It is occasionally seen in chest surgery during stripping of the periosteum. It is then of brief duration, and ceases without producing ill effect as soon as the stimulus is removed. This sensitivity is decreased with adequate premedication.

Caine and Reynolds[28] reported that electrocardiographic studies made in dogs and cats during ethylene anesthesia gave no evidence of disturbance in cardiac automaticity or conduction. Kurtz, Bennett and Shapiro[29] found that procaine or ethylene are the anesthetic agents giving the lowest incidence of arrhythmias in humans. Ethylene gives no marked stimulation or depression of the vagus center.[3] The heart rate may increase slightly during induction if excitement is present, but cardiac action remains clinically normal during maintenance. Blood pressure usually remains normal, or only slightly elevated, after an initial rise which may be seen during the rare occurrence of excitement.[30] Killian[31] found no change in the EKG, and a stable pulse and blood pressure under ethylene anesthesia. Both the vasomotor and respiratory centers are not affected if the gas is administered properly without hypoxia. Ethylene is not a stimulant of the parasympathetic system.

The study of blood changes under any anesthetic is dependent upon the amount of oxygen in the circulation. Therefore, all anesthetic agents should be administered without cyanosis, labored or depressed respiration, or other evidence of hypoxia.

From results obtained both in dogs and humans, Trout[32] concluded that ethylene-oxygen produces less alteration of the percentage of blood sugar, no appreciable change in either the coagulation time or the bleeding time, and only a slight disturbance of the native complement when compared with ether, chloroform, nitrous oxide-oxygen and regional (sacral) anesthesia. Leake and Hertzman[33] found that when there is no anoxemia, ethylene does not lower the p_H and carbon dioxide content of arterial blood beyond normal limits, while ether or chloroform cause a marked and rapid change. Lemann,[34] from a study made upon diabetics who had undergone major surgery, pre-

ferred ethylene, which at no time gave any occasion for anxiety due to the anesthetic.

Brumbaugh[35] concluded from a study of 15 humans that ethylene-oxygen caused no change in the hemoglobin, coagulation time or character of the blood clot; only slight temporary decrease of the carbon dioxide combining power of the blood; the blood sugar although immediately increased, very quickly returned to the preanesthetic level; no immediate increase in blood urea, and only a slight increase in 24 hours; and contrary to the observations of Yates and Raine[36] found no appreciable change in the icterus index, or derangement of the biliary system.

The results of Yates and Raine,[36] and also Oberhelman and Dyniewicz,[30] agreed with the acid-base balance observations of Leake and Hertzman.[33] Oberhelman, *et al.*, reported that the changes in the nonprotein nitrogen constituents of the blood were insignificant and within normal variations.

Ethylene has less toxic effect on the kidney parenchyma than has ether.[37] Asphyxia of even normal kidneys for short periods of time leads to more or less disturbance of kidney function. Therefore, this is another reason why the asphyxia which is an inherent hazard of all anesthetic agents and methods must be avoided. Brumbaugh[35] found on chemical and microscopic study that the urine was normal after ethylene-oxygen anesthesia. Walton[38] observed that ethylene did not affect significantly the chloride, urea, and phosphorus output, or dye excretion and water diuresis in dogs, and concluded that there was no appreciable decrease in the 24-hour urinary output.

Stander[39] reported that ethylene produced no demonstrable lesions in the kidney. He also stated that anoxemia alone caused degenerative changes in liver cells.

Histologic examinations of body tissues after repeated administrations of ethylene over long periods of time were made by Bouchaert,[40] Franken and Miklós.[41] No more than a slight amount of congestion or fatty change in the parenchymatous tissue could be found. It is generally believed that, in the absence of anoxia, ethylene has little significant effect on general metabolic activity. Prothrombin deficiency does not appear in the normal dog following ethylene anesthesia.[42] Reynolds[43] observed no significant pathology on microscopic examination of kidneys, adrenals, hearts and lungs of white mice that had been repeatedly exposed to ethylene.

While ether and chloroform anesthesia in dogs gave complete inhibition of the contractions of the stomach, small intestines and colon, during which there was a distinct lowering of muscular tone, Miller and Plant[44] found that light ethylene anesthesia caused an increase in the amplitude of the contractions, without change in tone in the same viscera. In deep ethylene anesthesia, or after the removal of the anesthetic, the contractions decreased or rapidly returned to normal.

Johnson and Ivy[45] reported that ethylene depressed gastric secretion in man, but not to the same extent as ether. It also delayed the emptying time of the stomach.

CLINICAL EXPERIENCE

Ethylene has been employed in this institution during 18,250 operations. Ethylene-oxygen alone has been the anesthetic in 11,560 instances. Table II

TABLE II

Ethylene-oxygen	11,591
Ethylene-oxygen-ether	4,720
Nitrous oxide-oxygen to ethylene-oxygen	238
Local plus ethylene-oxygen	483
Spinal plus ethylene-oxygen	792
Continuous spinal plus ethylene-oxygen	33
Spinal plus ethylene-oxygen-ether	19
Avertin plus ethylene-oxygen	288
Avertin plus ethylene-oxygen-ether	21
Vinethene to ethylene-oxygen	5
Cyclopropane-oxygen to ethylene-oxygen	9
Ethylene-oxygen to cyclopropane-oxygen plus ether	9
Ethylene-oxygen plus intocostrin	2
Splanchnic block plus ethylene-oxygen	38
Pentothal plus ethylene-oxygen	2
	18,250

illustrates the frequency of the use of ethylene with other agents. Although ethylene combines satisfactorily with other anesthetic agents, a study of such a combination makes for confusion in attempting the evaluation of any one agent. For that reason, a detailed study has been made of only the patients who received ethylene-oxygen alone. The data herein presented concerns the last 3,210 consecutive patients where ethylene-oxygen alone was employed. The results obtained in this series are comparable to our previous experience.

There were no fires or explosions in the entire series of 18,250 anesthesias.

ETHYLENE-OXYGEN ALONE

There were no anesthetic deaths in our series. The very low incidence of anesthetic deaths with ethylene is illustrated by reports from Henson,[46] which appears in Table III. This includes the anesthetics given in 38 New York City hospitals during a four-year period. In a later report he[47] stated that ethylene seems to be unquestionably the best of the anesthetics in present use, and that the use and application of this fact would save many lives.

TABLE III

ANESTHETIC DEATHS IN OPERATING ROOMS—NEW YORK CITY

Four-year Survey (1937)

Agent	No. of Anesthesias	Deaths Per 100,000
Ether	513,560	15
Nitrous oxide	188,820	13
Cyclopropane	12,707	15
Ethylene	31,426	0
Chloroform	3,842	25
Ethyl chloride	810	493
Spinal	91,263	42
Local	146,976	11

Since this is a teaching institution, our series of anesthetics has been administered by a large number of inexperienced anesthetists working under supervision. The group of 3,210 ethylene-oxygen anesthetics being analyzed were administered by 91 physicians, including teaching personnel, anesthesia residents, and rotating surgical interns in addition to a large number of junior and senior medical students. This fact must be considered in evaluating the results.

TABLE IV

OPERATIONS UNDER ETHYLENE-OXYGEN ALONE

Head—Intracranial	16
Head—Others	128
Neck—Thyroids	200
Neck—Others	152
Chest—Superficial	184
Radical mastectomy	139
Operations upon thoracic cage	29
Lung abscess, empyema, thoracostomy	40
Thoracoplasty or plumbage	191
Intrathoracic (heart, lung, mediastinum, esophagus)	141
Abdomen—Superficial	57
Intra-abdominal (upper)	33
Repair ventral hernia	17
Intestinal resection	24
Closure of colostomy	11
Appendicectomy	23
Inguinal or femoral herniotomy	59
Intra-abdominal gynecology	11
Miscellaneous anal and perineal	227
Operations upon adrenals	5
Bladder and ureter	10
Suprapubic prostatectomy	4
External genitalia	48
Perineph. abscess and miscellaneous lumbar	20
Nephrectomy	52
Nephrostomy and nephropexy	33
Bones, joints and tendons	1325
Nerves	31
Total	3210

This group was composed of 1,503 male and 1,707 female patients. Their age variation was:

1– 9 years = 101	30–39 years = 573	60–69 years = 239
10–19 years = 645	40–49 years = 543	70–79 years = 74
20–29 years = 603	50–59 years = 422	80–99 years = 10

Premedication: It is necessary to lower the metabolic rate with premedication to increase the potency of the gas and still maintain adequate oxygen in the blood. Apprehension should also be prevented.

Under ordinary circumstances atropine has no place in ethylene anesthesia, since it is not irritating to either the mucous membranes or the cardiovagus activity.

Morphine sulfate Gm. 0.010 to 0.015 hypodermically, and calcium nembutal Gm. 0.18 to 0.27 in 50 cc. of water per rectum, both administered one

to 1.5 hours before anesthesia were found to be very satisfactory for adults. The barbiturate prevented apprehension yet rarely caused confusion or depressed respiration. This, no doubt, contributed greatly to a smooth induction. A wide variety of other types of premedication were occasionally employed.

Table IV presents the type of surgery in which ethylene-oxygen alone was used.

Table V presents in detail the 50 deaths that occurred following the 3,210 operations, making a mortality rate of 1.5 per cent. There were no deaths in the operating room. It is of interest that the preoperative risk on the 50 patients was recorded as follows: Good, one; fair, seven; poor, 19; serious, 16; emergency (poor), six; semimoribund, one. The cause of death in most instances was determined at autopsy. Very few, if any, of the deaths were related to the anesthesia. The 13 deaths following thoracic surgery were considered by the surgeons to be adequately explained on the basis of the severity of the disease, and/or, the surgical procedure. Likewise, all the deaths from uremia were in patients who had uremia before anesthesia.

Very major surgical operations were performed under ethylene-oxygen anesthesia. In this series were 141 intrathoracic operations upon the heart, lung, mediastinum and esophagus. This includes the first successful resection of the lower esophagus and esophagogastrostomy for carcinoma performed through the thorax. This was made on January 26, 1938, by Dr. D. B. Phemister, assisted by Doctors W. E. Adams, H. N. Harkins, H. Wilson and J. Post. The patient was a 53-year-old female, in fair preoperative condition. An uneventful ethylene-oxygen mask anesthesia was administered by Dr. G. Light, with a positive pressure type of anesthesia apparatus. Chart 1 illustrates the satisfactory postoperative course. The patient is without evidence of recurrence at the present time.

In order to evaluate the use of ethylene-oxygen in a group of patients who are poor surgical risks, a study of 191 thoracoplasties was made. One hundred and five male and 86 female patients comprised this group. The age variation was: one to nine years, one; ten to 19, seven; 20 to 29, 48; 30 to 39, 87; 40 to 49, 32; 50 to 59, nine, and 60 to 69, seven. The preoperative risk was: Fair 72; poor, 81; serious, 37; and special, one. Table VI presents the postoperative complications that occurred. The circulatory complications were not related to anesthesia. The 27 instances of postoperative oxygen want were explained by the extensive collapse made by the surgical procedure. The 12.5 per cent incidence of postoperative nausea and vomiting occurred in 20 of the 25 instances only on the day of operation and was no doubt due both to anesthesia and morphine. Four patients (2 per cent) had retention or cystitis. The same number were given too much postoperative sedation with respiratory-depressing drugs. The minor respiratory complications included three hiccough and six cough. One accidental pneumothorax and two instances of pleural effusion were surgical complications. One contralateral spread of pulmonary tuberculosis may have been due to both anesthesia

TABLE V

DEATHS

Total No. Ops.	Operation	No. of Deaths	%	Risk	Op. Day	Cause and Time of Death					
						1–3 Days	4–7 Days	7–14 Days	14–21 Days	Within 1 Month	Within 2 Months
16	Head—Intracranial	1	.03	Emerg. (poor)			Brain abscess				
15	Mastoid	1	.03	Poor				Meningitis			
200	Neck—Thyroid	1	.03	Poor		Luetic aortitis					
152	Neck—Others	3	.09	2 Fair; 1 serious		Infection	Coronary	Hodgkin's			
191	Thoracoplasty	5	.15	1 Poor; 4 serious	Circulatory failure	Pul. tbc.	Pul. tbc.; metab. dis.		Br. Pn.		
141 Intra-thoracic	Thoracotomy, *etc.*	3	.09	1 Poor; 2 serious		Ca. lung; cerebral thrombosis					Uremia
	Pneumonectomy	1	.03	Poor				Ca. lung.			
	Lobectomy	2	.06	Poor				Circulatory failure		Pul. edema	
	Esophagus	2	.06	Poor			Circulatory failure; pul. emb.				
33	Intra-abd. (upper)	2	.06	Fair; emerg. (poor)		Common duct obst.		Ca. stomach			
3	Op. upon pancreas	2	.06	Fair; emerg. (poor)		Peritonitis; circulatory failure					
24	Intestinal resection	4	.12	2 Poor; 2 serious	Coronary occlusion	Circulatory failure	Coronary	Peritonitis			
5	Adrenal ops.	2	.06	Fair; poor		Adrenal insuff		Infection			
7	Cystotomy	1	.03	Emerg. (poor)			Septicemia				
4	Suprapubic prostectomy	1	.03	Poor				Uremia			
26	Nephrostomy	5	.15	2 Poor; 1 serious; 2 emerg. (poor)	Uremia	2 Uremia			Uremia	Uremia	
227	Miscellaneous anal or perineal	4	.12	1 Fair; 3 serious			Carcinoma	Circulatory failure		Septicemia	Carcinoma
1349	Bones, joints, tendons, *etc.*	10	.3	1 Good; 1 fair; 4 poor; 3 serious; 1 semimoribund	Coronary; traumatic shock	A-S gangrene; diabetes mellitus	Hemorrhage		Cerebral thromb.; leukemia; coronary	Uremia	Coronary emb.
Totals		50	1.5		5	14	10	9	5	4	3

and surgery. The one instance of bronchopneumonia occurred over two weeks after anesthesia. The high fever was explained on the basis of the disease.

TABLE VI

191 THORACOPLASTIES—POSTOPERATIVE COMPLICATIONS

Complication	Total No.	Per Cent	Op. Day	Time 1–3 Days	4–7 Days	7–14 Days	14–21 Days	Within 1 Month
B.P. fall marked (not shock)	3	1.5	2		1			
Traumatic shock	6	3.0	6					
Tachycardia	3	1.5		3				
Fibrillation	1	.5		1				
Transfusion reaction	1	.5			1			
Moderate secondary anemia	2	1.0		1		1		
Overdose postop. depressing drugs	4	2.0		4				
Oxygen-want moderate	22	11.0	13	8				1
Oxygen-want severe	5	2.5	2	1	1		1	
Hiccough	3	1.5	1		1	1		
Cough	6	3.0	3			2	1	
Pleural effusion	2	1.0				2		
Accidental pneumothorax	1	.5		1				
Contralateral pul. tbc	1	.5			1			
Broncho,neumonia	1	.5					1	
Nausea and vomiting	25	12.5	20	4	1			
Diaphoresis	1	.5		1				
High fever	16	8.0	3	10	1	1	1	
Debility	2	1.0			1	1		
Psychosis	2	1.0				2		
Headache	1	0.5		1				
Positional neuritis	1	0.5		1				
Retention or cystitis	4	2.0		2	1	1		
Moderate wound infection	6	3.0			1	4	1	
Severe wound infection	1	0.5						1

Since pulmonary tuberculosis was a definite factor in evaluating postoperative complications another group containing many poor risk patients not having tuberculosis was studied. This included 200 thyroidectomies performed upon 35 male and 165 female patients with mask anesthesia. The preoperative risks were: Good, 79; fair, 81; poor, 30; serious, eight; and special, two. The age variation was: Ten to 19 years, six; 20 to 29 years, 36; 30 to 39 years, 47; 40 to 49 years, 61; 50 to 59 years, 36; 60 to 69 years, nine; and 70 to 79 years, five.

The complications during and following anesthesia appear in Table VII.

A notably low incidence of circulatory and respiratory complications occurred in these patients, many of whom had preoperative cardiovascular disease and underwent surgery which has inherent possibilities of interference with, or damage to, the respiratory passages.

In order to eliminate the factor of surgical interference with respiration, the 139 radical mastectomies were reviewed. The preoperative risks were: Good, 65; fair, 56; poor, 14, and serious, four. The age distribution was:

Twenty to 29 years, two; 30 to 39 years, 20; 40 to 49 years, 44; 50 to 59 years, 37; 60 to 69 years, 23; 70 to 79 years, 12; and over 80 years of age, one. Table VIII presents the incidence of complications during and follow-

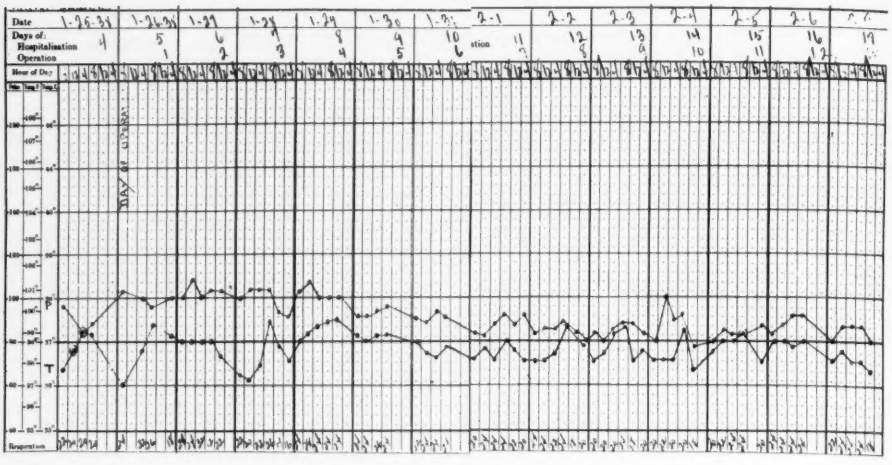


CHART I.—Showing postoperative course.

TABLE VII

200 THYROIDECTOMIES—COMPLICATIONS

During Anesthesia	Number	Per Cent	Postoperative	Number	Per Cent
Hypertension	8	4.0	Coronary	1	.5
Moderate hemorrhage	3	1.5	Moderate hemorrhage	5	2.5
Traumatic shock	1	.5	Circulatory failure	1	.5
Hypotension	1	.5	Fibrillation	6	3.0
Bradycardia	1	.5	Tachycardia	3	1.5
Tachycardia	6	3.0	Thyroid crisis	1	.5
Fibrillation	1	.5	Cystitis	1	.5
Nausea or emesis	9	4.5	Nausea and emesis	26	13.0
Cough	6	3.0	Diarrhea	1	.5
Moderate oxygen-want	6	3.0	Moderate oxygen-want	1	.5
Severe oxygen-want	2	1.0	Respiratory depression	1	.5
Moderate stridor	2	1.0	Cord paralysis	1	.5
Tracheal compression	1	.5	Upper respiratory infection	1	.5
Diaphoresis	3	1.5	High fever	11	5.5
Insufficient premedication	6	3.0	Trauma to eye or skin	2	1.0
			Headache	2	1.0
			Cerebral embolus; thrombosis	2	1.0

ing surgery, which indicates a very low morbidity rate from anesthesia. There may be some direct stimulation of the vomiting center by ethylene, but this occurred no more frequently than with nitrous oxide or cyclopropane, and it was minimal in comparison with ether. Prolonged nausea and emesis after ethylene was rare. A great deal depended upon the amount of morphine the patients received.

SUMMARY

Laboratory and clinical results indicate that ethylene-oxygen seems to be definitely the preferable inhalation agent for the poor-risk patient, including those with disturbed cardiopulmonary mechanisms. The reported death rate with ethylene is apparently lower than with any other inhalation agent.

Ethylene is deficient in providing deep abdominal relaxation for the average patient. It has the same inherent explosive quality that is present in all inhalation agents except chloroform or nitrous oxide.

Clinical experience inclines the author to believe, with Poe,[48] that we

TABLE VIII

139 RADICAL MASTECTOMIES—COMPLICATIONS

During Anesthesia	Number	Per Cent	Postoperative	Number	Per Cent
Insufficient premedication	4	2.8	Idiosyncrasy narcotic	1	.7
Bradycardia	2	1.4	Arrhythmia	1	.7
B.P. fall marked (not shock)	9	6.3	B.P. fall marked (not shock)	1	.7
Traumatic shock	3	2.1	Traumatic shock	1	.7
Moderate hemorrhage	1	.7	Moderate hemorrhage	1	.7
Hypertension	3	2.1	Transfusion reaction	2	1.4
Respiratory depression	5	3.5	Respiratory depression	2	1.4
Moderate oxygen-want	1	.7	Phlebitis	2	1.4
Respiratory obstruction	1	.7	Retention	1	.7
Cough	2	1.4	High fever	5	3.5
Nausea	7	4.9	Nausea	2	1.4
Emesis	5	3.5	Emesis	25	17.5
Diaphoresis	5	3.5	Chronic tonsillitis	1	.7
			Moderate wound infection	5	3.5

should give our patients the advantages and safety of this superior anesthetic, and that it merits more widespread employment, particularly for many operations in the patients classed as "poor surgical risks."

REFERENCES

1 Priestley, Joseph: Experiments and Observations Relating to Various Branches of Natural Philosophy: With a Continuation of the Observations on Air. Vol. I—The Appendix, No. VIII, pp. 474–479. Printed for J. Johnson, London, March 1, 1779.

2 Luckhardt, A. B., and Lewis, Dean: Clinical Experiences with Ethylene-Oxygen Anesthesia. J. A. M. A., **81**, 1851–1857, December 1, 1923.

3 Luckhardt, A. B., and Carter, J. B.: The Physiologic Effects of Ethylene: A New Gas Anesthetic. J. A. M. A., **80**, 765–770, March 17, 1923.

4 Brown, W. E.: Preliminary Report Experiments with Ethylene as a General Anesthetic. Canadian Med. Assoc. Jr., **13**, 210, March, 1923.

5 Bevan, A. D.: Ethylene Gas Anesthesia. Tr. Am. Surg. Assoc., Phila., **41**, 435–443, 1923.

6 Luckhardt, A. B., and Carter, J. B.: Ethylene as a Gas Anesthetic. J. A. M. A., **80**, 1440–1442, May 19, 1923.

7 Lundy, J. S.: Personal communication.

8 Guthrie, D., and Woodhouse, K. W.: Safety Factors in Ethylene Anesthesia. J.A.M.A., **114**, 1846–1850, May 11, 1940.

[9] Alessandri, R.: Ethylene. Arch. ital. di chir., **22,** 709–710, 1929.

[10] Goméz, G. Esquerra: Ethylene: Results in 500 Operations. Rev. méd. de Colombia, **2,** 508–513, May, 1932.

[11] Meana, T. A., and Elder, R. O.: 1000 Anesthesias with Ethylene, Cyclopropane and Nitrous Oxide. Semana méd., **2,** 959–965, October 21, 1937.

[12] Palma, E. C.: Ethylene: New Gas for Surgical Anesthesia. An. Fac. de med. de Montevideo, **26,** 1–132, 1941.

[13] Escobar, R. Lucca: Ethylene. Bol. hosp. Caracas, **42,** 171–270, September-December, 1943.

[14] Dautrebande, L.: Ethylene. Liége méd., **31,** 137–151, February 6, 1938.

[15] Booth, H. S., and Campbell, M. B.: Studies of Anesthetic Ethylene: The Odor of Ethylene. Anesth. and Analg., **8,** 221–226, July-August, 1929.

[16] The Hazard of Explosion of Anesthetics. J. A. M. A., **94,** 1491–1498, May 10, 1930.

[17] Livingstone, H., Shank, I., and Engel, R.: Fire and Explosion Hazard with Anesthetic Agents. Hospitals, **13,** 36, July, 1939.

[18] Greene, B. A.: The Hazard of Fire and Explosion in Anesthesia. Anesthesiology, **2,** 144–160, March, 1941.

[19] Coryllos, Pol N., and Birnbaum, G. L.: Studies in Pulmonary Gas Absorption in Bronchial Obstruction. Am. J. Med. Sc., **183,** 317–359, 1932.

[20] Grollman, A.: The Solubility of Gases in Blood and Blood Fluids. J. Biol. Chem., **82,** 317–325, May, 1929.

[21] Nicloux, M., and Yovanovitch, A.: L'anesthésie par l'éthylene: Dosage de l'anesthésique dans le sang. Compt. Rend. des Séances et Mémoires de la Soc. de Biol., **93,** 1653–1656, 1925.

[22] Seevers, M. H., DeFazio, S. F., and Evans, S. M.: A Comparative Study of Cyclopropane and Ethylene: With Reference to Body Saturation and Desaturation. J. Pharm. & Exper. Therap., **53,** 90–104, January, 1935.

[23] Orcutt, F. S., and Waters, R. M.: The Diffusion of Nitrous Oxide, Ethylene and Carbon Dioxid Through Human Skin During Anesthesia. Anesth. and Analg., **12,** 45–47, January-February, 1933.

[24] Leake, C. D., Lapp, H., Tenney, J., and Waters, R. M.: Effects of Anesthetics on Osmotic Resistance of Erythrocytes: II. Nitrous Oxide or Ethylene with Oxygen. Proc. Soc. Exper. Biol. and Med., **25,** 93–94, November, 1927.

[25] Adams, W. E., Thornton, T. F., Carlson, A. J., and Livingstone, H. M.: Anoxia and Anesthesia in Intrathoracic Operations. Surgery, **13,** 859–879, June, 1943.

[26] Guedel, A. E.: Inhalation Anesthesia: A Fundamental Guide. The Macmillan Co., New York, Part II, Chapt. IV, pp. 99–106, 1937.

[27] Taylor, I. B.: Cyclopropane Anesthesia: With a Report of the Results in 41,690 Administrations. Anesthesiology, **2,** 641–653, November, 1941.

[28] Caine, A. M., and Reynolds, C.: Electrocardiographic Studies of the Action of Propylene and Some Other Anesthetic Gases. Soc. Exp. Biol. & Med., **23,** 488, March, 1926; *idem, ibid.:* **26,** 1925.

[29] Kurtz, C. M., Bennett, J. H., and Shapiro, H. M.: Electrocardiographic Studies During Surgical Anesthesia. J. A. M. A., **106,** 434–441, February 8, 1936.

[30] Oberhelman, H. A., and Dyniewicz, H.: A Metabolism Study of Ethylene Anesthesia. J. A. M. A., **83,** 2012–2014, December 20, 1924.

[31] Killian, H.: Untersuchungen über die höheren Gasnarkotika der Kohlenwassertoffreihe. Schmerz Narkose-Anaesthesia, **3–4,** 121–159, 1930–32.

[32] Trout, H. H.: Blood Changes Under Ethylene Anesthesia. Anesth. & Analg., **8,** 269–275, September-October, 1929.

[33] Leake, C. D., and Hertzman, A. B.: Blood Reaction in Ethylene and Nitrous Oxid Anesthesia. J. A. M. A., **82,** 1162–1165, April 12, 1924.

34 Lemann, I. I.: Anesthesia in Diabetics: Report of Observation on the CO_2 Combining Power of the Blood Plasma Before and After Ethylene Anesthesia in Diabetics Protected with Insulin. Anesth. and Analg., **10**, 142–144, May-June, 1931.

35 Brumbaugh, J. D.: Effects of Ethylene-Oxygen Anesthesia on the Normal Human Being. J. A. M. A., **91**, 462–465, August 18, 1928.

36 Yates, J. L., and Raine, F.: The Untoward Effects of Narcotics and Anesthetics upon Robust and Handicapped Patients. ANNALS OF SURGERY, **87**, 124–129, January, 1928.

37 Luckhardt, A. B., and Kretschmer, H. L.: Ethylene Anesthesia in Genito-urinary Surgery. Jr. of Urology, **11**, 415–424, April, 1924.

38 Walton, R. P.: Effect on Kidney Function of Ether, Ethylene, Ethylene and Sodium Isoamyl-ethyl Barbiturate (Amytal) and Ethylene and Tribromethyl Alcohol (Avertin). J. Pharm. & Exp. Therap., **47**, 141–149, February, 1933.

39 Stander, H. J.: Studies in Anesthesia, Anoxemia, Anhydremia and Eclampsia: With Certain Deductions Concerning the Treatment of Eclampsia. Am. J. Obst. & Gynec., **12**, 633–654, 1926.

40 Bouchaert, J. J.: Influence de l'éthylène sur les échanges respiratoires, la pression sanguine et le coeur isolé. Compt. Rend. des Séances et Mémoires de la Soc. de Biol., **91**, 907–909, 1924.

41 Franken, H., and Miklós, L.: Experimentelle Untersuchungen über die Frage der Organschäden nach Gasnarkosen (Acetylen, Äthylen und Stickoxydul), Zentralbl. f. Gynäk., **57**, III, 2493–2498, October, 1933.

42 Allen, J. G., Kable, V., and Livingstone, H.: Effects of Anesthetic Agents on Prothrombin Concentrations in Experimental Animals. Anesth. and Analg., **20**, 156–159, May-June, 1941.

43 Reynolds, C.: Comparative Studies of Propylene, Ethylene, Nitrous Oxide and Ether. Jr. Pharm. & Exper. Therap., **27**, 93–99, March, 1926.

44 Miller, G. H., and Plant, O. H.: The Effects of Nitrous Oxide, Ethylene, Ether and Chloroform on the Contractions of Stomach, Small Intestines and Colon during General Anesthesia. J. Pharm. & Exp. Therap., **25**, 147–148, 1925.

45 Johnston, R. L., and Ivy, A. C.: Contributions to the Physiology of Gastric Secretion: XI The Effect of Ethylene Anesthesia on Gastric Secretion and Motility. Am. Jr., Physiol., **78**, 104–109, September, 1926.

46 Henson, C. W.: The Relative Safety of Anesthetics. Anesth. and Analg., **16**, 349–358, November-December, 1937.

47 Henson, C. W.: A Review of Established Anesthetics: With Analysis of Deaths in New York City for Five-Year Period. N. Y. State Jour. Med., **36**, April 1, 1936.

48 Poe, J. G.: Ethylene Anesthesia. J. A. M. A., **105**, 66, July 6, 1935.

ACOUSTIC TRAUMA

H. B. PERLMAN, M.D.

CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY (DIVISION OF OTOLARYNGOLOGY), UNIVERSITY OF CHICAGO, CHICAGO, ILL.

ONE may think of trauma as due only to direct contact between the primary force and some part of the body. However, it may be pointed out that the force may originate at some distance and be propagated to the body like a sound wave through the surrounding medium (air, water). An important example is the blast wave.

The peripheral ear is a mechanism especially constructed to respond to pressure (sound) waves propagated by the molecules of the air at the rate of about 1,100 feet per second. The normal stimulus for the ear represents an exceedingly small pressure disturbance. When these pressure waves are sufficiently great they may traumatize the exquisitely delicate neutral elements suspended in the fluid of the labyrinth.

Acoustic trauma (boiler maker's deafness, explosion deafness, *etc.*) is a term used here to denote injury to the neural elements of the ear by noise. The war has aroused general interest in this cause of deafness, because so many people are exposed to the great noises associated with modern warfare.

Noise has been an uncontrollable by-product of modern industrial civilization and modern warfare. While we have known in a general way for the past 100 years that noise is harmful to the ear, it is only during the last decade that any real progress was made in recognizing this kind of deafness and devising means for preventing it.

This report deals only with the effect of noise on the auditory sense but it is well to point out that many other harmful effects of noise have been observed, such as the effect on working efficiency, mental function,[1] *etc.*

The audiometer has been a great help in the study of this as well as other otologic problems. With the audiometer one can measure and record quantatively in decibels the hearing acuity for just audible sounds over a wide range of frequencies. The widespread use of the audiometer soon brought to light many cases of hearing loss not suspected by the subject. One type of hearing loss was characterized by an abrupt high tone drop in the threshold curve or by an isolated drop around 4,096 cycles per second. Careful investigation often indicated that the subjects had been exposed to loud noise. Audiometric examinations of large numbers of people known to have been exposed in this way, were made recently by Bunch,[2] Larsen,[3] Rosenblith,[4] and others. These studies help to establish firmly the relationship between this early defect in hearing and excessive stimulation.

Noise may be defined as the sound sensation due to acoustic waves occurring at random intensity and frequency. In contrast, pleasing sound sensation is due to regularly recurring acoustic pressure waves. It is rare that the latter are sufficiently intense to cause deafness.

The analysis of noise is facilitated by modern acoustic, electronic instruments such as the wave analyzer, improved microphones, noise level meter, *etc.* A measure of the intensity and frequency of the component sounds in a particular noise is often made possible with such tools. Some difficulty remains in recording very brief acoustic pressure waves—such explosive noise as may be described as a pop, bang or crack, *etc.* The major disturbance may last only about 1/1000 of a second in these noises and it is difficult to devise apparatus that will faithfully follow such rapid phenomena (Fig. 1).

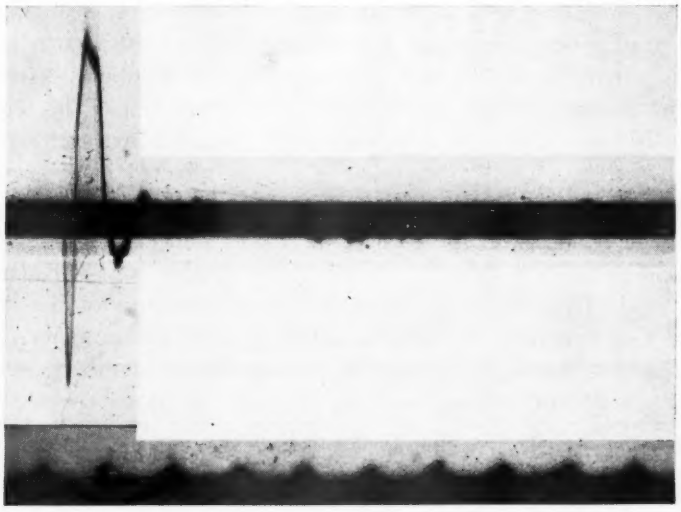


FIG. 1.—Record of movement of the human middle ear mechanism (at the malleus) to explosive noise. Note that major reaction is over in 1/1000 second. T is a 1000 cycle per second timing wave.

Clinical experience has indicated some of the noises that are harmful to the ear, *i.e.,* the noise of pneumatic hammers such as those used in rivetting and chipping steel, noise of various kinds of motors and turbines, noise of metal stamping machines, drop forges, and the noises from discharging firearms, and explosions of various kinds. Single shocks to the ear as from a telephone or from a blow on the ear can also damage the end-organ.

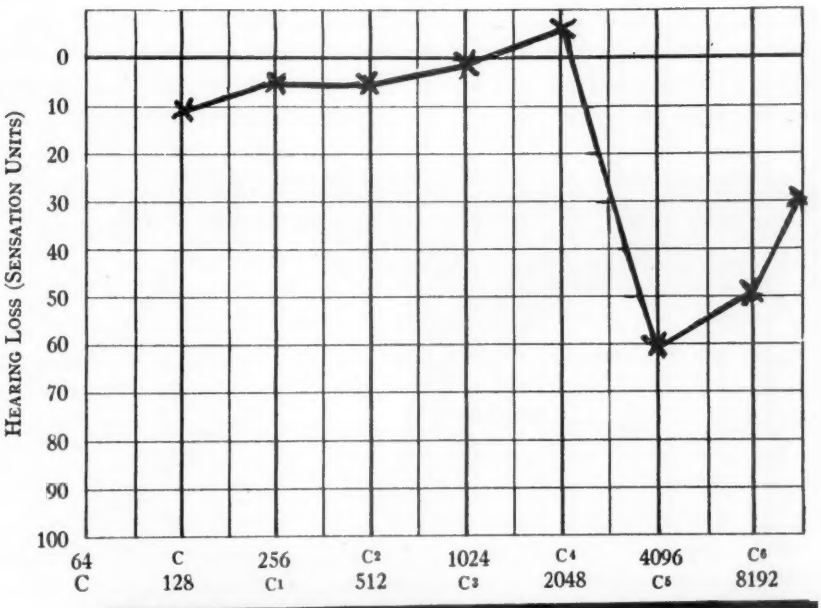
Many occupations are known to be associated with impaired hearing, *i. e.,* boiler makers, steel workers of other kinds, aviators, machinists, engineers, *etc.* While many industrial operations are exceedingly noisy, few studies have been made in the factory because of the fear of employers that medicolegal suits may follow. The problem has been recognized by some legal bodies and rates of disability and compensation have been worked out that are based on the results of the audiometric examination. The most important use we make of our auditory sense is for understanding speech. The frequencies tested for in the audiometric examination vary greatly in their importance for hearing the human voice. Tests show that we can hear sounds varying in frequency from 20 to 20,000 cycles per second. It is exceedingly important

for speech perception to hear well through the frequency range between 500 and 2,000 cycles per second. Considerable deafness above or below this range will have very little effect on our ability to understand speech. The ear is more sensitive through this range of sound in many different ways. The intensity needed to elicit a threshold response is much less than at a lower or higher range. Also through this frequency range we recognize more differences in loudness and in pitch as the intensity and frequency of the sound is changed. Another property of the auditory sense may be mentioned: That is the ability of the cortex to fill in gaps in the auditory spectrum. Controlled experiments show that only a narrow band of frequencies through this range is needed to understand speech. A familiar example of this cortical phenomenon is the ability to hear speech over a very poor telephone system—where most of the acoustic energy of a speaker at the other end of the line may not reach the listener—and only a narrow band around 1,000 cycles per second may reach the ear. Intelligibility is not greatly affected in spite of this distorted acoustic spectrum. The threshold curve obtained with the audiometer really measures only the capacity to hear. The cortex may compensate for considerable peripheral defect. Furthermore, people vary greatly in their demands on the auditory sense, *i.e.*, a musician is much more demanding than a laborer. Consequently, the clinician cannot predict the amount of complaint by looking at the audiogram alone. It is also important to understand that speech is carried out ordinarily at an intensity of 40 to 60 decibels above threshold. With ordinary acuity, one can understand a low conversational voice easily at some distance from the speaker even against the background of considerable noise. Even when the threshold curve indicates a loss of 10 to 25 decibels, not too much handicap results, because the listener will ordinarily be close enough to the speaker to receive a sufficiently intense stimulus from an average speaker. As the threshold curve drops to 30 decibels, and below, the ability to converse is much more affected because the speaker must now be less than three feet from the ear of the listener to deliver adequately strong stimuli—while using a moderate voice. It is impractical to carry on conversation at such close range or at a greater speech intensity. A small change in the hearing ability after it has dropped to the 30 decibel level, will, therefore, be very noticeable to the patient in his ability to converse with others.

With this general background of the auditory sense one may proceed to consider some of the factors involved in the deafness due to acoustic trauma. In the clinic, the diagnosis may be made after careful elimination of other possible causes, when the audiogram shows the particular characteristics described above. On the other hand, the diagnosis is relatively simple, if one examines a group of employees in a noisy industry. The high tone loss does not progress after the subject ceases to be exposed. Tinnitus, however, may continue. Deafness may fluctuate with relation to the immediate period of exposure. Considerable recovery takes place within hours after exposure.

It is well to remember that after early childhood our auditory spectrum gradually shrinks from the high frequency end. This natural aging of our

FIG. 2



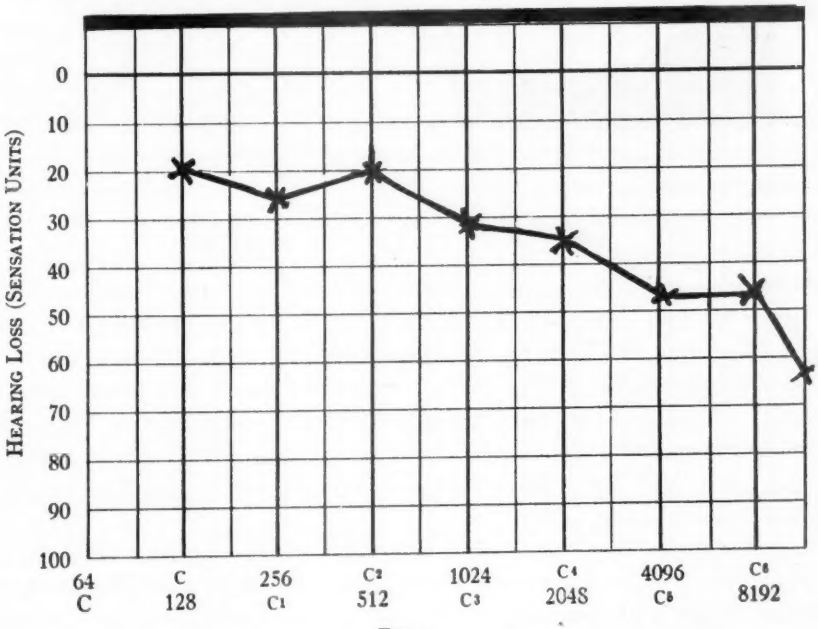


FIG. 3

FIG. 2.—Audiogram typical of early acoustic trauma. Such as may follow exposure for several hours to great sustained noise (i.e. aircraft engine) or exposure to a single explosive noise.

Hearing for the conversational voice may not be affected.

FIG. 3.—Audiogram typical of advanced acoustic trauma. Such as may follow working as a riveter for ten years.

Hearing for the conversational voice would be noticeably affected.

auditory sense organs must be taken into account in the interpretation of our tests. The first evidence of trauma usually appears as a sharply localized dip in the threshold curve between 4,000 and 6,000 cycles per second (Fig. 2). At this time the subject may experience no difficulty in hearing. As trauma continues, hearing for the still higher frequencies is affected, but again very little noticeable effect will occur to the subject. Then the hearing for sounds

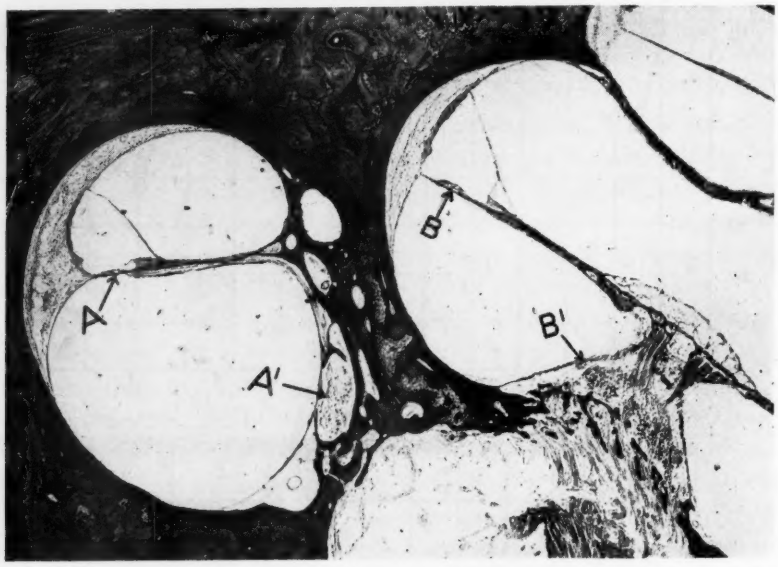


FIG. 4.—Photomicrograph (×32) of the human cochlea illustrating the pathology of the end-organ in acoustic trauma.
A. Degeneration of the organ of Corti in the basal coil with associated degeneration of the spiral ganglion cells A'.
The organ of Corti in the middle coil is more normal (B) and the ganglion cells in the spiral ganglion B' more numerous and healthier.

below 4,000 cycles per second becomes affected, and with this loss difficulty in understanding some speech sounds (consonants and whispered voice) are noted (Fig. 3). The pathologic findings, within the limitations of the method of microscopic examination of the end-organ, are clearly defined changes in the cochlea. They include degeneration of the outer hair cells of the organ of Corti and throwing off of the cells below the basilar membrane. Degeneration of the inner hair cells and secondarily of the spiral ganglion occur with greater trauma (Fig. 4).

Analysis of a large number of cases of acoustic trauma examined in the light of our present knowledge of acoustics and audition indicates a great number of factors influencing the degree of deafness that is seen in acoustic trauma. Some of these factors are:

1. Total time of exposure.
2. Length of exposure in each period.
3. Loudness of the noise.
4. Distance from the source.

5. Age of the subject.
6. Individual differences in susceptibility to acoustic trauma.
7. Duration of the major sound waves.
8. The character of the surroundings in which the noise is produced.
9. The position of each ear with respect to the sound source.
10. The use of protective devices.
11. Previous ear disease.
12. Frequency pattern of the noise.

One of the investigations carried on in this laboratory concerned this last factor, *i.e.*, The relation of the frequency of the traumatizing sound to the degree and type of the resultant deafness.[5] This investigation showed that for equal intensities, low frequency sounds are much less traumatizing than high frequency sounds. Furthermore, the greatest hearing loss was found to be an octave above the frequency of the traumatizing sound. A sharp dip in the threshold around 4,000 cycles per second typical of early acoustic trauma, could be produced only by exposing a subject to a sound of 2,000 cycles per second. It is important to know that exposure to very loud low frequency sounds does not injure the hearing while similar exposure to higher frequency sounds is definitely harmful. With our present knowledge of the ear, one cannot explain the greatest depression occurring an octave above the traumatizing sound. Furthermore, we cannot explain why the 4,096 dip in the audiogram appears in almost every clinical case of early acoustic trauma, regardless of the type of traumatizing noise.

With the development of the science of acoustics, much is being done to protect us from harmful noise. In general, these efforts are directed along three different phases: 1. Elimination of noise at its source. 2. Reducing noise by altering the surroundings. 3. Protection to the ear itself by various obturators, *etc.* Cooperation of the industrial engineer, acoustic physicist and otologist will help to minimize this undesirable by-product of modern civilization.

REFERENCES

[1] McCord, C., Teal, E. E., and Witheridge, W.: Noise and Its Effect on Human Beings. J. A. M. A., **110**, 1553–1560, May 7, 1938.

[2] Bunch, C. C.: Diagnosis of Occupational or Traumatic Deafness: Historical and Audiometric Study, Laryngoscope, **47**, 615–691, September, 1937.

[3] Larsen B.: Investigation of Professional Deafness in Shipyard and Machine Factory Laborers. Acta. Otolaryng., Supp. **36**, 3–255, 1939.

[4] Rosenblith, W. A.: Industrial Noise and Industrial Deafness. J. Acoustical Society of America, **13**, No. 3, 220–225, January, 1942.

[5] Perlman, H. B.: Acoustic Trauma in Man. Arch. Otolaryng., **34**, 429–452, September, 1941.

RESECTION OF THE LEFT LOBE OF THE LIVER IN A PATIENT WITH FOUR SEPARATE CARCINOMAS

JOHN VAN PROHASKA, M.D.

CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF ILLINOIS, CHICAGO, ILLINOIS.

WITHIN RECENT YEARS surgeons have extended the operability of cancer, not only within the original site of involvement, but also in the regional and distant metastases. Although many surgeons have resected parts of the liver for various reasons, the subject of the resection of the left lobe of the liver has not been adequately described in the literature. O. H. Wangensteen[1] describes the surgical problems of gastric cancer, with special reference to close coincidental hepatic resection. Other than this, the present surgical literature appears to be scanty. J. Gautier[2] resected the quadrate lobe of the liver for a primary carcinoma, and Benson and Penberthy[3] reported on a surgical excision of a primary tumor of the liver in an infant seven months old, with survival.

The purpose of this paper is to present my experience with the resection of the left lobe of the liver in a man who had four separate and distinct carcinomas. Inasmuch, as the indications for the resection of the left lobe of the liver is so well illustrated in this case, I feel it would serve this paper best if I presented the case history first.

Case Report.—The patient, a white male, age 47, was first seen in September, 1939. At this time he complained of gradual and progressive loss of weight over a period of four months, abdominal distress and pain in the right lower quadrant. The physical examination revealed a tender mass in the right lower quadrant, which was firm and freely movable. The roentgenologic examination revealed an obstructive lesion at the cecum. The patient was operated upon in September, 1939, and a large carcinoma of the cecum was found at celiotomy. Approximately 30 cm. of the terminal ileum, the cecum, the ascending colon, the hepatic flexure and a part of the transverse colon with a corresponding V-shaped segment of the mesocolon were resected. An ileotransverse colon-colostomy was then performed.

The patient made an uneventful recovery and left the hospital two weeks after the operation. In September, 1941, a roentgenogram of the large bowel revealed a normal functioning bowel, without evidence of malignant neoplasm (Fig. 1). At this time he had no abdominal complaints. The patient continued to enjoy good health until December, 1944, when he returned to the hospital, complaining of a rather rapidly growing tumor in the region of the right cheek, just over the zygoma. This, he stated, had been present for about two months. The clinical impression was squamous cell carcinoma of the face. This mass was excised by a rather large elliptical resection, and postoperative roentgenotherapy was administered. The microscopic diagnosis was a squamous cell carcinoma.

During the course of this interview it was noted that the patient had lost about 15 pounds in weight, and that he complained of vague abdominal distress, marked by flatulence, distention and cramp-like pain. This was associated with an occasional bloody stool. The physical examination was negative. Roentgenograms of the large bowel

revealed a complete obstruction to the retrograde flow of barium a few centimeters below the splenic flexure. The diagnosis of carcinoma of the splenic flexure (Fig. 2) was made, and the patient was again operated upon.

The abdomen was opened through a large transverse incision. A few centimeters below the splenic flexure a tumor-mass, measuring about ten centimeters in diameter, was encountered. No lymphatic metastases were felt in the omentum or the mescolon. However, in the region of the left lobe of the liver, high in its dome, there was a small, firm umbilicated mass which one could feel within the substance of the liver.

FIG. 1.—Barium enema two years after resection of carcinoma of cecum.

It was situated in a position where a biopsy would have been most difficult. My impression was that this was a solitary metastases to the left lobe of the liver. Almost the entire transverse colon, the splenic flexure, and a generous share of the descending colon were resected (Figs. 3 and 4). The previous ileocolostomy was found in a good condition, and the small segment of the transverse colon in this area was left behind to afford a good end-to-side anastomosis between it and the sigmoid colon. It was also thought that sparing a segment of the transverse colon would afford better reabsorption of minerals and fluids.

The patient again made an uneventful recovery. He left the hospital in two weeks and returned a week later for the resection of the left lobe of the liver. This procedure will be described separately. About four months after the partial resection of the liver, the patient returned with a small nodule in the skin on the posterior aspect of his neck. This was found to be a squamous cell carcinoma, his fourth separate cancer.

The operation of left hemihepatectomy was performed as follows: It was noted at the previous operation that a transverse incision would not afford the optimal exposure for the left lobe. Therefore, a high midline incision was made extending from the xyphoid down, and slightly to the left of the umbilicus. It was thought that if adequate exposure could not be obtained by this incision, that the incision could be extended transversely. This, however, was not necessary. Upon opening the abdomen the nodule in the left lobe of the liver, previously described, was again noted.

FIG. 2.—Roentgenogram of colon showing carcinoma of splenic flexure.

The coronary ligament of the liver on the left side was divided as well as the ligamentum teres. This latter was used as a handle and greatly facilitated the mobilization of the liver. The cutting of the coronary ligament alone gave an excellent mobilization of the liver. A row of interrupted chromic No. 1 catgut was then placed at about one centimeter from the groove dividing the right and left lobes of the liver. Following this, another row of interrupted catgut sutures were placed in an interlocking fashion. The liver to the left of the two rows of suture was then resected, using scissors. It was possible to feel greater resistance with the scissors at certain points, and when this increased resistance was felt, an additional hemostat was placed before further progress was made in cutting the liver off. Only one large arterial bleeder was encountered, and this was readily caught with an ordinary hemostat. A perfect hemostasis was accomplished after three separate bleeders were ligated over hemostats. A slight serosanguineous fluid continued to discharge from the cut-surface of the liver. Part of the ligamentum teres, the triangular ligament, and a part of the coronary ligament, as well

as the neighboring fat and the omentum, were utilized to cover the raw surface of the liver. Five grams of crystalline sulfanilamide and a cigarette drain were inserted into the operating field, and the wound was closed in the usual fashion. The patient made an uneventful recovery except for a moderate discharge of clear, serous, bile-stained fluid

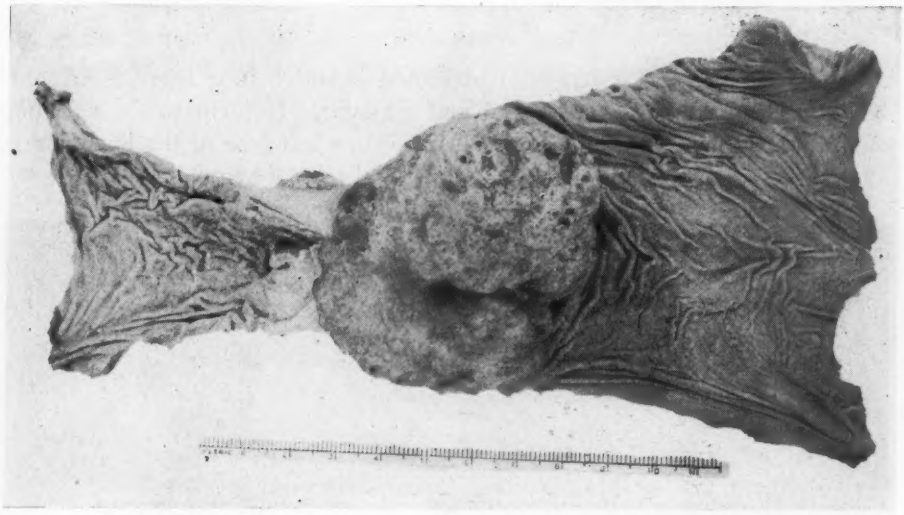


FIG. 3.—Part of the gross specimen of the carcinoma of splenic flexure.

FIG. 4.—Photomicrograph of the carcinoma of the splenic flexure.

from the drainage tract. This continued in diminishing amounts for about three weeks. Three days after his operation his urine was negative; leukocyte count 14,000; icterus index 6; nonprotein nitrogen 30. The patient was discharged from the hospital 12 days after the operation. He continued to improve in a normal convalescent fashion.

Three months after the operation he was back at work, had gained 15 pounds in weight, and was apparently enjoying good health. He returned four months after this operation with a nodule, a squamous cell carcinoma of the posterior aspect of the neck previously described. The resected specimen of the liver weighed 240 Gm. (Fig. 5). The nodule, which we considered to be a solitary metastasis, was found to be, on microscopic examination, an area showing marked focal proliferation of bile ducts with cholangiectasis and focal hepatitis.

In conclusion, a case has been presented in which four separate and different carcinomas have been found and removed. Incident to the resection of the splenic flexure a nodule was found in the left lobe of the liver which, after resection of this lobe, proved to be a focal area of hepatitis.

FIG. 5.—Segments of liver removed (after fixation). The specimens on the left show areas of focal hepatitis.

The indications for the resection of the left lobe of the liver are clearly indicated in this case, if one disregards the final microscopic diagnosis of the liver nodule resected with the lobe. This was peculiar in this particular case because preliminary biopsy of the liver nodule was technically impossible. This nodule had to be considered carcinomatous because of the location of the original tumor in the left half of the colon, and because on palpation it felt like an ordinary metastatic nodule. I felt that, inasmuch as there were no palpable intervening lymphatic metastases, and no other palpable nodules in the right lobe of the liver that the removal of a solitary metastatic nodule

in the left lobe of the liver would afford the patient a chance for a longer survival. Certainly, this same thought is carried out in the operation of radical mastectomy where the original tumor, the breast, the underlying muscles, and the axillary content are removed *en bloc*.

This singular experience indicates that it is possible to resect the left lobe of the liver, with an adequate exposure and good hemostasis. In so doing, one may further extend the operability of cancer in certain well-indicated instances.

REFERENCES

[1] Wangensteen, O. H.: Arch. Surg., **46**, 879–906, June, 1943.
[2] Gautier, J.: Mem. Acad. de Chir., **68**, 274–275, June, 1942.
[3] Benson, C. D., and Penberthy, G. C.: Surgery, **12**, 881–886, December, 1942.

THE ETIOLOGY AND TREATMENT OF POLYCYTHEMIA RUBRA VERA*

OBSERVATIONS BASED UPON STUDIES OF BODY FLUID CHANGES IN DOGS SUBJECTED TO PROPRIOCEPTOR DEPRESSOR NEUROTOMY AND EXTENSIVE SYMPATHECTOMY, INCLUDING THE CASE REPORT OF A MAN WITH POLYCYTHEMIA RUBRA VERA TREATED BY EXTENSIVE PARAVERTEBRAL SYMPATHECTOMY

PAUL W. SCHAFER, M.D.

CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF CHICAGO, CHICAGO, ILL.

POLYCYTHEMIA is a term frequently used to denote an elevation of the red blood cell count without regard for the size of the cells or their hemoglobin content and with no consideration of the total red cell mass. The various classifications of this state, which have been proposed, are based chiefly on the relation of the red cell mass to the plasma volume and total blood volume. "Relative polycythemia" may be said to occur when the red cell count is elevated because of loss of plasma from the blood, *i.e.,* as in burns, however, hemoconcentration is a more common designation. In this condition, the red cell mass remains normal, or less than normal, and the plasma volume and total blood volume are decreased. "Absolute polycythemia" indicates an actual increase in the red cell mass either with or without an increase in total blood volume. The absolute polycythemias are usually considered to be of two types: First, "erythrocytosis" or "secondary polycythemia" in which, in response to known etiologic factors, the red cell mass is increased, usually without marked increase in total blood volume; and, second, "erythremia" or "polycythemia rubra vera," a disease of as yet uncertain etiology characterized by a marked increase in total blood volume due almost entirely to increase in red cell mass, the plasma volume usually being within normal limits.

In all types of secondary polycythemia, that is, absolute polycythemia due to the action of known stimuli, there is a similarity in that all of these conditions present a defect in oxygenation of the systemic arterial blood. The exact means by which this deficient oxygenation of the blood stimulates the production of increased numbers of red blood cells by the bone marrow is not known, however, the fact remains that in conditions characterized by decreased oxygenation of the systemic arterial blood, whether it be due to a shunting of venous blood of low oxygen tension through the patent foramen ovale of congenital heart disease or to inhibition of the respiratory function of immature red cells as occurs after the administration of cobalt,[1] the bone marrow responds by the production of more red cells. Thus, we see increase in the red cell mass in the following conditions: congenital heart disease with defective auricular or ventricular septi, patent foramen ovale or patent ductus arteriosis, some cases of mitral stenosis, pulmonary fibrosis

* This work was done on grants from the Douglas Smith Foundation and from Mr. Joseph O. Hanson.

and emphysema, sclerosis of the pulmonary artery (Ayerza's disease), residence at high altitudes, and following poisoning by many chemicals, the action of all of which has not been as thoroughly studied as has that of cobalt. One of the most severe cases of secondary polycythemia we have seen was that of a man 24 years of age, who was found to have a cavernous hemangioma of the left lung with a functioning arteriovenous shunt. This case has been reported in detail elsewhere.[2]

Vaquez reported the first case of polycythemia rubra vera, or erythremia, in 1892,[3] with further observations in 1895.[4] During the next few years numerous cases were recorded in the literature, Osler's papers in 1903 and 1904 arousing considerable interest.[5] Turk,[6] 1900 and 1904, first pointed out the leukocytosis seen so commonly in association with erythremia and also emphasized the peripheral blood picture evidence for hyperplasia of both the leukopoietic and erythropoietic elements of the myeloid tissue.[7, 8] As a result of these original observations plus numerous case reports made in the first decade of this century, erythremia became recognized as a disease entity characterized by increase in the red cell mass and total blood volume with frequent evidence of general hyperactivity of the marrow elements. The disease is somewhat intermittent in character but is slowly progressive, with eventual fatality, due usually to thrombosis of major or vital vessels. The half century that has passed since its original description has seen the contribution of descriptive literature and some improvements have been made in the therapy of the condition, but few important observations have been made either on the nature of the condition or on its etiology. Thus, as has been indicated, polycythemia rubra vera became recognized as a disease entity, but little is known of its etiology.

Our interest in the subject of polycythemia was aroused by observations made on dogs which were being studied for what, at that time, was thought by us to be a completely unrelated condition—hypertension. The basis for our experiment was as follows: The carotid sinus and cardio-aortic proprioceptive nerves constitute the afferent limbs of a reflex arc that is of fundamental importance in regulation of the blood pressure. Impulses are known to pass centripedally through these nerves to the vasomotor centers of the brain stem from which areas efferent impulses course outward to the heart and blood vessels of the body by way of the sympathetic nerves and the vagus. This reflex mechanism exerts its control of the circulation in part, by alteration of cardiac function but its major influence is brought about through variation of peripheral vascular tone. Thus, by experimental tampering with the afferent proprioceptive and the efferent vagal and sympathetic nerves, one is able to induce various acute and chronic changes in peripheral vasomotor tone. This, at once, opens up a broad field for investigative work, much of which has been done, as is evidenced by many brilliant reports since Claude Bernard's original description of vasoconstrictor fibers in 1852.[9] However, most of this work has concerned acute effects related to alteration of the caliber of peripheral vessels and much of it has dealt solely with

changes in blood pressure. We were intrigued by the prospect of observing animals maintained in states of chronic peripheral vasoconstriction and vasodilation, and our first interest was not so much with the effect of this chronic alteration of vasomotor tone on blood pressure as it was to record changes in certain of the body fluids. This report is in part based on those observations.

The cardio-aortic depressor nerve was first described by Cyon and Ludwig, in 1866.[10] It is composed of purely afferent fibers which are depressor in function. These fibers terminate at various points in the wall of the aorta and heart and are generally considered to be vagal in origin since in most animals they are indistinguishably bound within the sheath of the vagus nerve and pass to the medullary centers together with other fibers of the vagus. In the rabbit, these cardio-aortic depressor fibers are collected into a separate nerve that joins the vagus high in the cervical region. In 25 per cent of dogs they form a separate nerve lying in the vagosympathetic trunk between the vagus laterally and the sympathetics medially. In most dogs, however, the fibers are not grossly identifiable. The carotid sinus is a slight enlargement in the region of the bifurcation of the common carotid artery, although in many cases it solely involves the commencement of the internal carotid. The carotid sinus nerve is a branch of the glossopharyngeal which terminates in the wall of the carotid sinus. It, like the cardio-aortic nerve, is purely afferent and depressor in function.

Both of these proprioceptive nerves bear end-organs situated in the walls of the vessels supplied. These end-organs are of two types: presso-receptor and chemoreceptor, the former being by far the more significant. The presso-receptors discharge impulses when they are mechanically stimulated by stretching of the vessel wall as it is subjected to increased pressure. The chemoreceptors are stimulated by oxygen lack or carbon dioxide excess. By oscillographic methods both the carotid sinus and cardio-aortic nerves have been shown to discharge impulses centrally at varying rates, the rate increasing with elevation of blood pressure and decreasing with fall of blood pressure. During the cardiac cycle, for example, the greatest frequency of discharge occurs during systole and the least during diastole.[11] Thus, these nerves continuously bombard the medullary centers with depressor impulses of such frequency as to maintain a constant normal blood pressure. From the medullary centers cardio-accelerator, cardio-inhibitory, vasoconstrictor and vasodilator impulses pass to the periphery by way of various sympathetic and vagal pathways. In 1923, Hering[12] first showed that acute hypertension could be produced in rabbits by section of both the carotid sinus and cardio-aortic depressor nerves. His efforts to produce chronic hypertension did not meet with as much success. In 1931, Heymans[13] reported the successful production of chronic hypertension in dogs by a similar operation. To Hering and to Heymans, their coworkers and students, should go much of the credit for the present day understanding of the physiology of these regulator nerves.

METHODS

As we approached our problem we knew from the experience of ourselves and others that a chronic vasoconstriction could be produced by ablation of the afferent depressor pathways which have just been described.[14] It was planned to produce chronic vasodilatation by extensive sympathectomy. Healthy adult dogs were used exclusively. To produce chronic peripheral vasoconstriction we used our modification of the original Heymans-Hering operation.[15] With aseptic technic, under light ether anesthesia, the neck was opened in the midline and the right vagosympathetic trunk and right carotid bifurcation visualized. First, the sheath of the vagosympathetic trunk was incised and an attempt made to identify the right cardio-aortic depressor nerve. As has been mentioned, in 25 per cent of the animals the nerve could be identified as a slender filament lying between the vagus laterally and the sympathetic trunk medially. If the nerve could be identified, it, together with the sympathetic fibers were sectioned and a segment excised. However, in most instances, accurate recognition was not possible, so an alternate method was used. This consisted of isolation of a rather constant, dense, white core of fibers in the centrolateral part of the vagus trunk. In many postmortem dissections we had determined that the fibers composing this core were distributed to areas below the level of the heart and, thus, could not contain afferent cardiac fibers. This isolated core of vagal fibers was preserved and the remainder of the vagosympathetic trunk together with its sheath divided and a segment excised. The carotid bifurcation was then visualized and ligatures tied about the internal, external and common carotid arteries approximately two centimeters in each direction from the bifurcation. The abundant fibers of the carotid sinus nerve were included in one of the superior ligatures. The entire carotid bifurcation was then excised within the area limited by the ligatures. The same procedure was then carried out on the left side except that on this side the entire vagosympathetic trunk was divided and a segment excised. The pertinent effect of this operation is interruption of all of the cervical afferent depressor pathways. With the loss of incoming depressor impulses the medullary centers are without inhibition. Thus, they send out a preponderance of cardio-accelerator and vasoconstrictor impulses resulting in an increase in heart rate and a marked peripheral vasoconstriction. Hypertension is the obvious result. We do not wish to make a detailed description of the blood pressure changes that occur in these animals except to indicate that this vasoconstriction can be easily demonstrated by increased resistance to perfusion of the distal end of a severed major peripheral artery and to point out that in our experience the hypertension is maintained, usually at a high level, for as long as we have observed our animals (several animals have been under observation for more than four years).[15]

Chronic peripheral vasodilatation was brought about by three-stage or two-stage radical paravertebral sympathectomy, ganglionectomy and splanch-

nicectomy. The first operation consisted of the transpleural resection of the left stellate ganglion, the entire sympathetic trunk including the sympathetic ganglia and the rami communicantes from the first thoracic to the first or second lumbar levels inclusively, together with all of the left splanchnic nerves and a considerable portion of the celiac ganglion. At the second operation, the right paravertebral region was approached transpleurally and a similar resection carried out. Both of these operations were performed under positive pressure intratracheal ether anesthesia with the animal in apnea. Since the second lumbar ganglia and their rami communicantes are apt not to be easily identified in all animals, in some of them it was necessary to do a third operation which consisted of the transabdominal resection of the remaining portions of the abdominal sympathetic trunk. As a result of these operations all of the efferent cardio-accelerator and vasoconstrictor pathways were interrupted and a loss of peripheral vasomotor tone occurred. This is manifest by hypotension. Due to some regeneration of nerve fibers and some local neuromuscular adjustments there is a tendency for these animals to recover some peripheral vascular tone but recovery is rarely complete and develops only slowly.

Our original aim was to study dogs prepared by the above methods from the standpoint of alteration in plasma volume, red cell mass, total blood volume, intra- and extracellular fluid and total body water with the animals maintained on standard kennel rations under constant laboratory conditions. Plasma volume was determined using our modification of the Gibson and Evans T-1824 dilution method, the blue dye concentration being determined in serum samples by the use of the Evelyn photo-electric microcolorimeter.[16] We had used this method extensively on both man and dogs and felt that under the conditions of our experiment a satisfactory degree of accuracy could be obtained. Red cell mass and total blood volume were calculated from the dye-determined plasma volume and the hematocrit. Reliable hematocrit readings were obtained using the Van Allen capillary tube without dilution and with centrifugation at 3,000 rpm. for 30 minutes. The volume of the extracellular fluid was approximated from dilution curves of sodium thiocyanate, using the method described by Crandall and Anderson.[17] Total body water was measured by means of sulfanilamide dilution curves and total blood water as described by Painter.[18] Both thiocyanate and sulfanilamide concentrations were read colorimetrically in the Evelyn photo-electric macrocolorimeter. Record was also made of the blood pressure, pulse rate, red blood cell count and the hemoglobin level. Twenty-nine normal mongrel dogs were used in the experiment. Ten of the dogs constituted a control group, and either were not subjected to surgery or died too soon after operation to warrant any conclusions as to the effect of the operation. Thirteen animals were made hypertensive and six were subjected to sympathectomy. All of the animals were observed for a sufficient length of time before and after operation to be certain of the validity of our results (Charts 2 and 3).

CONTROL OBSERVATIONS ON BODY FLUIDS

Observations made on all 29 of the dogs during the control period are summarized in Table I. Each figure in this chart represents the average of many determinations made during a one- to 16-month preoperative period in those dogs which were subsequently subjected to surgery and, in the case of several of the dogs which were retained as controls without surgery, the

TABLE I

Control and preoperative observations on 29 normal dogs. Each figure in this table represents an average of all designated readings made on each animal during a one to 16 months' period. Blood pressures are recorded in millimeters of mercury as mean arterial pressures obtained by needle puncture of the femoral artery.

DOG NO.	PLASMA VOLUME		RED CELL MASS		TOTAL BLOOD VOLUME		"AVAILABLE" FLUID		TOTAL BODY WATER		HEMATOCRIT	BL.PR.
	Total	cc/kgm.	Total	cc/kgm.	Total	cc/kgm.	Total	cc/kgm.	Total	cc/kgm.		
459	805	56	645	45	1445	101	4158	291	8370	589	44	136
597	622	54	690	58	1312	112	3485	325	6923	645	48	170
629	664	49	769	55	1433	104	3520	264	7723	579	53	159
453	606	51	642	54	1248	105	3495	293	7060	594	51	142
310	626	52	494	44	1120	96	2572	229	7388	651	44	145
400	478	58	388	46	866	104	2448	299	5810	704	45	147
330	340	49	256	36	596	85	2076	285	4528	652	43	131
305	632	54	545	47	1177	101	2943	245	6812	592	46	132
557	627	53	540	46	1167	99	3212	272	7226	608	46	143
111	1046	43	909	37	1955	80					46	140
598	592	52	600	51	1192	103	3085	268	7094	625	48	143
309	445	49	372	40	817	89	2088	226	5296	581	45	138
303	596	58	502	49	1098	107	2945	282	7039	690	49	138
307	751	53	799	54	1550	107	3726	257	8652	594	51	132
596	810	55	737	51	1547	106	4617	307	10643	710	47	150
627	654	55	600	52	1254	107	3665	308	7276	607	47	140
460	643	55	585	46	1228	101	3256	255	6864	564	48	148
220	616	57	502	47	1118	104	2910	261	7005	644	45	134
326	676	55	554	46	1230	101	3363	267	8244	676	45	141
394	540	54	490	42	1030	96	2999	284	6780	650	48	133
221	778	57	551	42	1329	99	3632	249	7927	593	42	132
21	604	57	447	40	1051	97	3046	286	6844	640	43	154
306	950	59	749	47	1699	106	4580	250	10760	672	44	124
327	500	56	419	48	919	104	2266	249	6281	713	45	130
624	730	52	777	54	1507	106	4160	292	9610	669	51	148
393	687	64	479	45	1166	109	3468	324	7594	705	41	136
277	780	58	602	45	1382	103	3784	274	8576	639	44	136
599	745	56	712	54	1457	110	4071	311	8577	659	49	149
625	818	49	785	48	1603	97	4777	350	10163	688	49	163
AVERAGE		54		47		101		279		640	46	142

figures represent many readings made during the course of one and one-half years of observation. Dog No. 394 is typical of the latter group. As may be seen from examination of Table I and Figures 1 and 2, the plasma volume varied from 43 to 64 cc. Kg. body weight, averaging 54 cc. Kg. of body

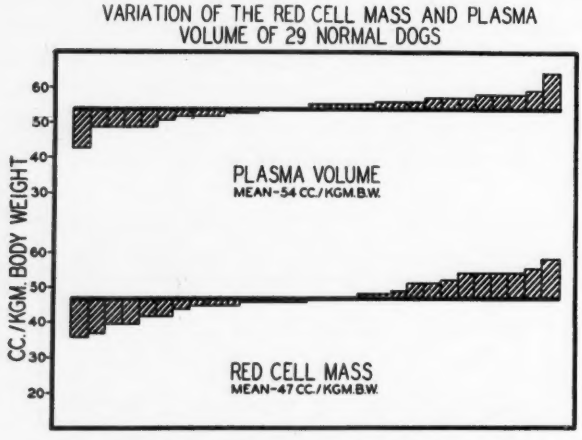


FIG. 1.—Variation of the red cell mass and plasma volume of 29 normal dogs expressed in cubic centimeters per kilogram of body weight. The solid horizontal lines represent the arithmetic means obtained for the entire group.

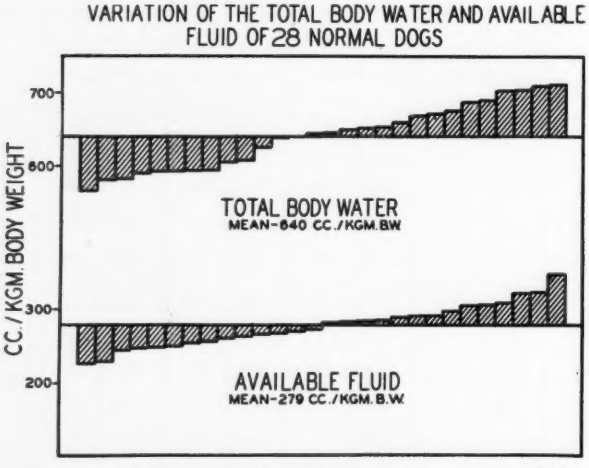


FIG. 2.—Variation of the "available fluid" and total body water of 28 normal dogs expressed in cubic centimeters per kilogram of body weight. The solid horizontal lines represent the arithmetic means obtained for the entire group.

weight, with most of the readings near the arithmetic mean. The higher values were uniformly encountered in the lean, rangy, short-haired dogs while the lower values were observed in the fat, stocky, long-haired animals. Essentially similar correlations held for the other body fluid levels. The red cell mass varied from 36 to 58 cc. Kg. of body weight, averaging 47 cc. The total blood volume varied from 80 to 112 cc. Kg. of body weight, averaging 101 cc. The "available fluid" varied from 226 to 350 cc. Kg. of body weight,

averaging 279 cc. The total body water varied from 564 to 713 cc. Kg. of body weight, averaging 640 cc. These findings are in agreement with the results of other writers who have used the same or similar methods. Although there was a fairly wide variation in these values in a group of dogs of varying build, for any given dog there was little fluctuation in the level of any of the body fluids so long as the animal was maintained on the standard kennel routine and did not become ill. This is indicated in the record of Dog No. 394 in Figure 3, which indicates less than a plus or minus 10 per cent deviation in plasma volume, red cell mass and total blood volume during a period of observation extending from February, 1941, to June, 1942. Fluctuations of

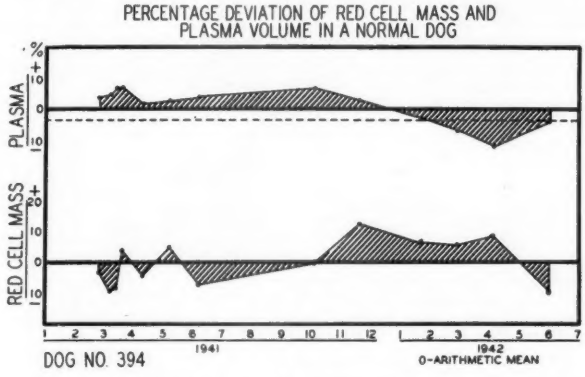


FIG. 3.—Fluctuation in red cell mass and plasma volume of a normal dog during one and one-half years of observation expressed as percentage deviation from the arithmetic mean of all determinations made on this animal.

similar magnitude were also observed in "available fluid" and total body water determinations in this particular animal. In the entire group of dogs: The hematocrit ranged from 42 to 53 per cent, averaging 46 per cent, while the mean arterial blood pressure ranged from 124 to 170 mm. of Hg., averaging 142 mm. of Hg.

BODY FLUID CHANGES FOLLOWING PROPRICEPTOR DEPRESSION NEUROTOMY

Plasma volume, red cell mass, and total blood volume determinations were made on all 13 of the dogs subjected to proprioceptor depressor neurotomy, while "available fluid" and total body water determinations were made on only eight. Evidence for the existence of chronic peripheral vasoconstriction in these dogs is the fact that following operation their average mean arterial blood pressure ranged from 160 to 301 mm. of Hg., averaging 216 mm. of Hg. for the group whereas before operation their blood pressures had ranged from 131 to 170 mm. of Hg., averaging 143 mm. Hg. for the group. Thus, the average mean arterial blood pressure for this group of 13 animals increased 51 per cent following proprioceptor depressor neurotomy. Each figure tabulated in Chart 2 and in Figures 4, 5, 6, 7 and 8 represents a level reached after the establishment of chronic peripheral vasoconstriction. From these data it may be seen that ten of the animals had a fall in plasma volume of from

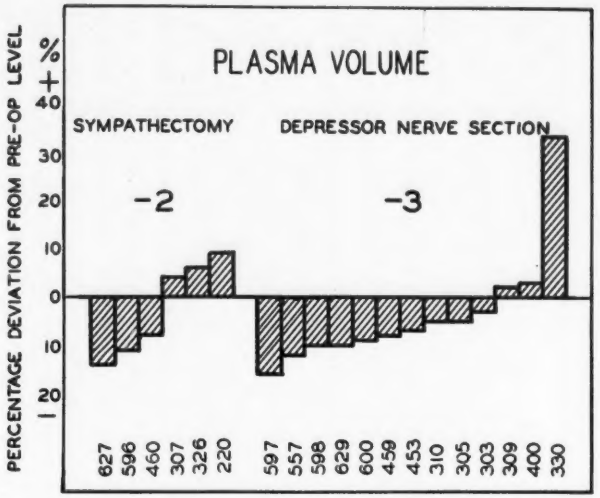

PLASMA VOLUME
PERCENTAGE DEVIATION FROM PRE-OP LEVEL
% + 40 30 20 10 0 10 20 −
SYMPATHECTOMY
DEPRESSOR NERVE SECTION
−2
−3
627 596 460 307 326 220
597 557 598 629 600 459 453 310 305 303 309 400 330

FIG. 4.—Changes in plasma volume observed following proprioceptor depressor neurotomy and extensive paravertebral sympathectomy expressed as percentage deviation from the average pre-operative level (0) for each animal. The dogs are identified by the numbers at the bottom of the chart. The average over all change for each group is indicated by the large numbers above the horizontal line.

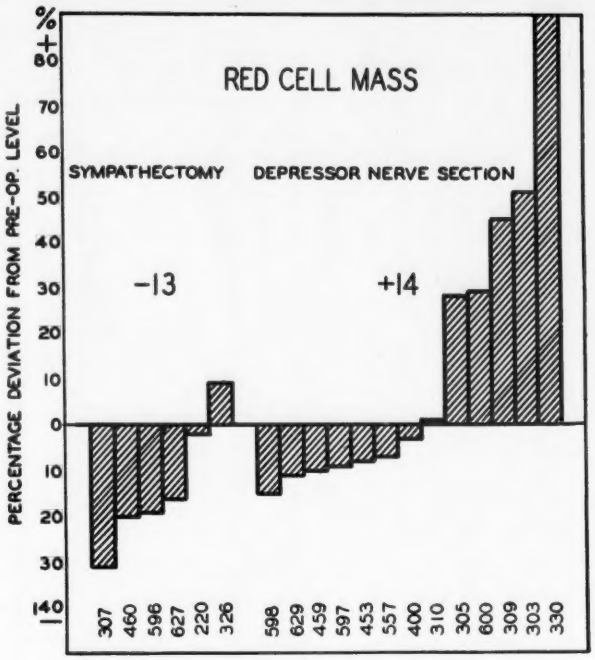


FIG. 5.—Changes in red cell mass observed following proprioceptor depressor neurotomy and extensive paravertebral sympathectomy expressed as percentage deviation from the average pre-operative level (0) for each animal. The dogs are identified by the numbers at the bottom of the chart. The average over all change for each group is indicated by the large numbers above the horizontal line.

Annals of Surgery
December, 1945

3 per cent to 16 per cent, and three animals an increase of 2 per cent, 3 per cent and 35 per cent, respectively, for an average over-all decrease in plasma volume of 3 per cent. Seven of the animals had a decrease in red cell mass of from 3 per cent to 15 per cent, and six animals an increase of from 1 per cent to 92 per cent, for an average over-all increase in red cell mass of 14 per cent. Eight of the animals had a decrease in total blood volume of from 2 per cent to 15 per cent, and five animals an increase of from 6 per cent to 59 per cent, for an average over-all increase in total blood volume of 4 per cent. Three of the animals had a decrease in "available fluid" of 1 per cent, 4 per cent and 6 per cent, respectively, and five animals an increase of from 1 per cent to 27 per cent, for an average over-all increase in "available fluid" of 8 per cent. Three of the animals had a decrease in total body water of 3 per cent, 7 per cent and 9 per cent, respectively, and five animals an increase of from 1 per cent to 19 per cent, for an average over-all increase in total body water of 2 per cent.

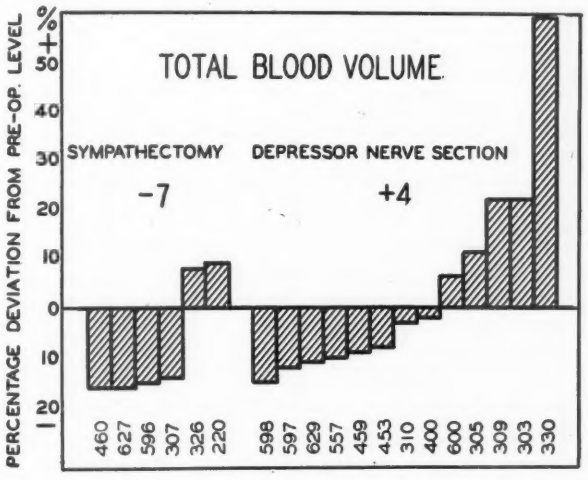


FIG. 6.—Changes in total blood volume observed following proprioceptor depressor neurotomy and extensive paravertebral sympathectomy expressed as percentage deviation from the average preoperative level (0) for each animal. The dogs are identified by the numbers at the bottom of the chart. The average over all change for each group is indicated by the large numbers above the horizontal line.

BODY FLUID CHANGES FOLLOWING EXTENSIVE PARAVERTEBRAL SYMPATHECTOMY

Plasma volume, red cell mass, total blood volume, "available fluid," and total body water determinations were made on all six of the dogs subjected to extensive sympathectomy. Following their last stage of sympathectomy the average mean arterial blood pressure of these animals ranged from 107 to 150 mm. of Hg., averaging 128 mm. of Hg. for the group, whereas, before operation their blood pressures had ranged from 132 to 150 mm. of Hg., averaging 141 mm. of Hg. for the group. Thus, the mean arterial blood pressure for this group of six animals decreased 9 per cent following operation. The detailed pressure changes for each animal are found in Table 3. This chart also indicates the changes observed in the various body fluids following sympathectomy. The mode of presentation is the same as described for Table 2. It may be seen that three of the animals had a decrease in plasma volume of 8 per cent, 11 per cent and 14 per cent, respectively, and three animals an increase of 4 per cent, 6 per cent and 9 per cent, respectively, for an average over-all decrease in plasma volume of 2 per cent. Five

TABLE II

Effect of proprioceptor depressor neurotomy on the blood pressure and body fluids of 13 dogs Each figure in this table represents an average level which was attained by the animal following this operation.

DOG NO.	WEIGHT (kgs.)	DURATION OF OBSERVATION (months)		AVERAGE BLOOD PRESSURE (mm. Hg)			PLASMA VOLUME (cc.)			RED CELL MASS (cc.)			TOTAL BLOOD VOLUME (cc.)			"AVAILABLE FLUID" (cc.)			TOTAL BODY WATER (cc.)		
		BEFORE PIN	AFTER PIN	BEFORE PIN	AFTER PIN	CHANGE %	BEFORE PIN	AFTER PIN	CHANGE %	BEFORE PIN	AFTER PIN	CHANGE %	BEFORE PIN	AFTER PIN	CHANGE %	BEFORE PIN	AFTER PIN	CHANGE %	BEFORE PIN	AFTER PIN	CHANGE %
598	11.6	5	10	145	301	+110	592	530	-10	600	510	-15	1192	1040	-15						
629	15.6	10	6	159	270	+70	664	595	-10	769	685	-11	1433	1280	-11						
459	15.4	2	11	156	206	+51	805	740	-8	645	580	-10	1445	1320	-9						
597	12.7	10	6	170	245	+45	622	520	-16	690	630	-9	1312	1150	-12						
455	15.2	2	16	142	215	+51	606	565	-7	642	585	-8	1248	1150	-8	5495	5550	-4	7060	7200	+2
557	11.5	2	9	143	212	+48	627	550	-12	540	500	-7	1167	1050	-10	5215	5050	-6	7226	7300	+1
400	8.9	5	1	147	174	+18	478	495	+3	388	357	-3	866	850	-2	2448	2480	+1	5810	6250	+8
510	12.3	2	2	145	191	+32	626	590	-5	494	500	+1	1120	1090	-3	2572	3120	+21	7588	6700	-9
505	10.6	2	4	132	201	+52	652	600	-5	545	700	+28	1177	1300	+11	2945	2900	-1	6812	6600	-3
600	22.6	2	6	140	160	+14	1046	950	-9	909	1170	+29	1955	2120	+8						
509	11.0	2	*6	138	198	+43	445	460	+2	372	540	+45	817	1000	+22	2088	2650	+27	5296	5600	+6
503	12.3	1	*6	138	279	+102	596	580	-3	502	760	+51	1098	1340	+22	2945	3420	+16	7059	6550	-7
550	7.6	1	6	131	164	+25	340	460	+35	256	490	+92	596	950	+59	2076	2350	+15	4528	5400	+19
AVERAGE						+51			-3			+14			+4			+8			+2

* See Figs. 9 and 10 for subsequent course.
PIN-Proprioceptor Depressor Neurectomy.

TABLE III

Effect of extensive paravertebral sympathectomy on the blood pressure and body fluids of six dogs. Each figure in this table represents an average level which was attained by the animal following this operation.

DOG NO.	WEIGHT (kgs.)	DURATION OF OBSERVATION (months)		AVERAGE BLOOD PRESSURE (mm. Hg)			PLASMA VOLUME (cc.)			RED CELL MASS (cc.)			TOTAL BLOOD VOLUME (cc.)			"AVAILABLE FLUID" (cc.)			TOTAL BODY WATER (cc.)		
		BEFORE SYM	AFTER SYM	BEFORE SYM	AFTER SYM	CHANGE %	BEFORE SYM	AFTER SYM	CHANGE %	BEFORE SYM	AFTER SYM	CHANGE %	BEFORE SYM	AFTER SYM	CHANGE %	BEFORE SYM	AFTER SYM	CHANGE %	BEFORE SYM	AFTER SYM	CHANGE %
507	15.7	5	12	152	150	0	751	780	+4	799	550	-31	1550	1330	-14	3726	4300	+15	8652	8600	-1
460	11.9	2	2	148	128	-15	645	594	-8	585	440	-20	1228	1035	-16	5256	5000	-8	6864	7150	+4
596	16.3	5	12	150	150	0	810	720	-11	737	600	-19	1547	1320	-15	4617	4750	+3	10643	8550	-20
627	11.9	4	11	140	133	-5	654	560	-14	600	500	-16	1254	1060	-16	3665	4050	+10	7276	5400	-26
220	11.5	3	*2	134	107	-20	616	670	+9	502	550	+9	1118	1220	+9	2910	3200	+10	7005	7000	0
526	12.4	2	*4	141	122	-13	676	720	+6	554	610	+10	1230	1330	+8	3363	3750	+11	8244	7900	-4
AVERAGE						-9			-2			-11			-7			+7			-8

* See Figures 11 and 12 for subsequent course.

of the animals had a decrease in red cell mass of from 2 per cent to 31 per cent, and one animal had an increase of 9 per cent, for an average over-all decrease in red cell mass of 13 per cent. Four of the animals had a decrease in total blood volume of from 14 per cent to 16 per cent, and two animals an increase of 8 per cent and 9 per cent, respectively, for an average over-all decrease in total blood volume of 7 per cent. One of the animals had a decrease of 8 per cent in "available fluid," while five of the animals had an increase of from 3 per cent to 15 per cent, for an average over-all increase of 7 per cent. Four of the animals had a decrease in total body water from 1 per cent to 26 per cent, one animal showed no change, and one animal had an increase of 4 per cent, for an average over-all decrease in total body water of 8 per cent.

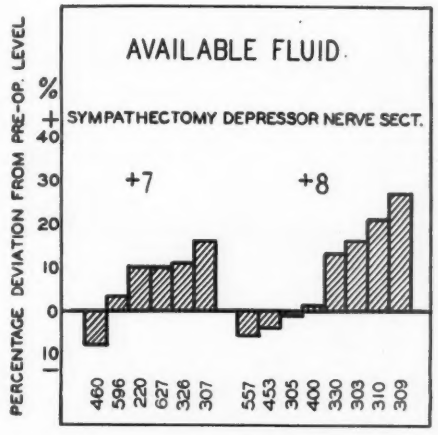


FIG. 7.—Changes in "available fluid" observed following proprioceptor depressor neurotomy and extensive paravertebral sympathectomy expressed as percentage deviation from the average preoperative level (O) for each animal. The dogs are identified by the numbers at the bottom of the chart. The average over all change for each group is indicated by the large numbers above the horizontal line.

In both of the foregoing groups of animals changes in hematocrit and hemoglobin determinations and red blood cell counts were observed to parallel the changes which have already been charted for the red cell mass. Some of these alterations will be shown later in the report.

PRELIMINARY CONCLUSIONS AND FURTHER EXPERIMENTATION

After comparison of the above data recorded after establishment of chronic peripheral vasoconstriction and chronic peripheral vasodilatation with the control and preoperative observations, we were of the opinion that significant changes had occurred in neither plasma volume or total body water. We felt that barely significant increases had occurred in the fluid available for the solution of sodium thiocyanate and that this increase was almost identical in both groups of animals. Since the plasma volume in the two groups had shown no alteration this indicated that in states of both vasoconstriction and vasodilatation slight but definite increase had occurred in the volume of the extracellular fluid, the change being of equal proportion in both groups of animals. The most striking alterations were observed in red cell mass and total blood volume. Four of the six animals subjected to sympathectomy showed substantial decrease in red cell mass and total blood volume as great or greater than that observed following proprioceptor depressor neurotomy. Also, six of the 13 animals subjected to proprioceptor depressor neurotomy showed spectacular increases in red cell mass reaching levels far greater than had been observed to occur spontaneously in the preoperative period in any animal or during the entire period of observation of the control

animals. We also felt that the average difference in red cell mass between the two groups of animals was of significance, the dogs with chronic peripheral vasodilation having an average 11 per cent decrease and the dogs with chronic peripheral vasoconstriction having an average 14 per cent increase in red cell mass.

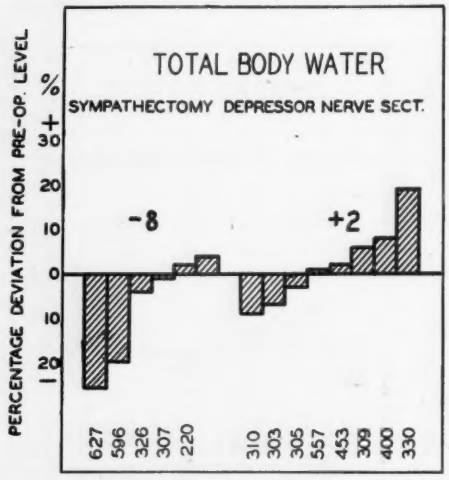
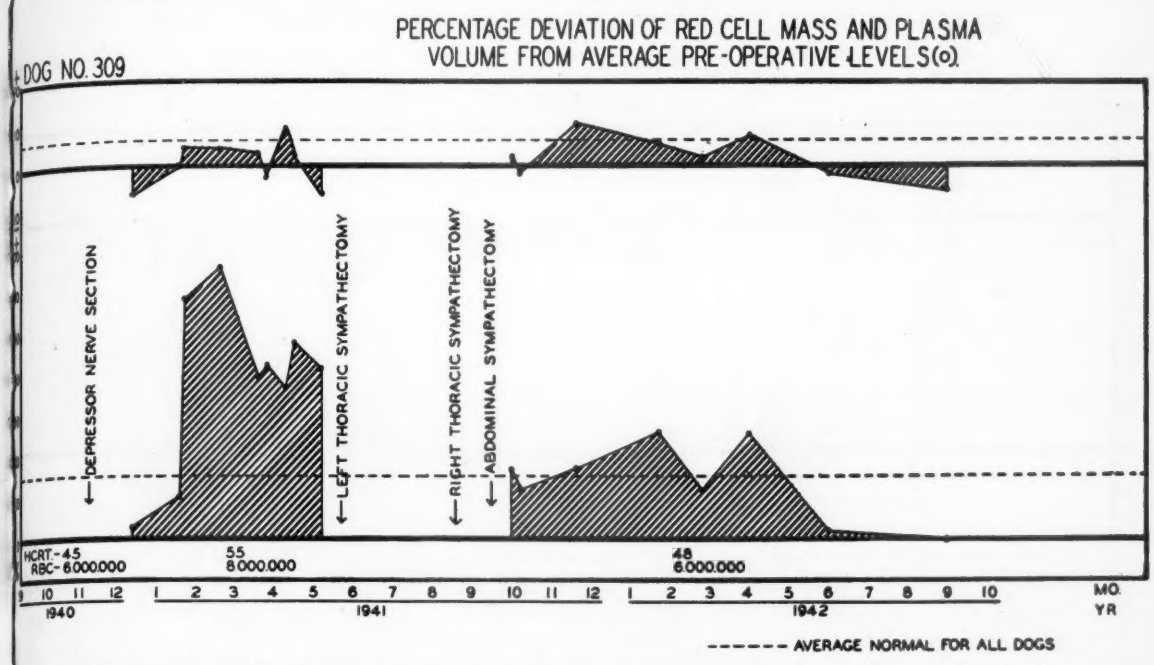
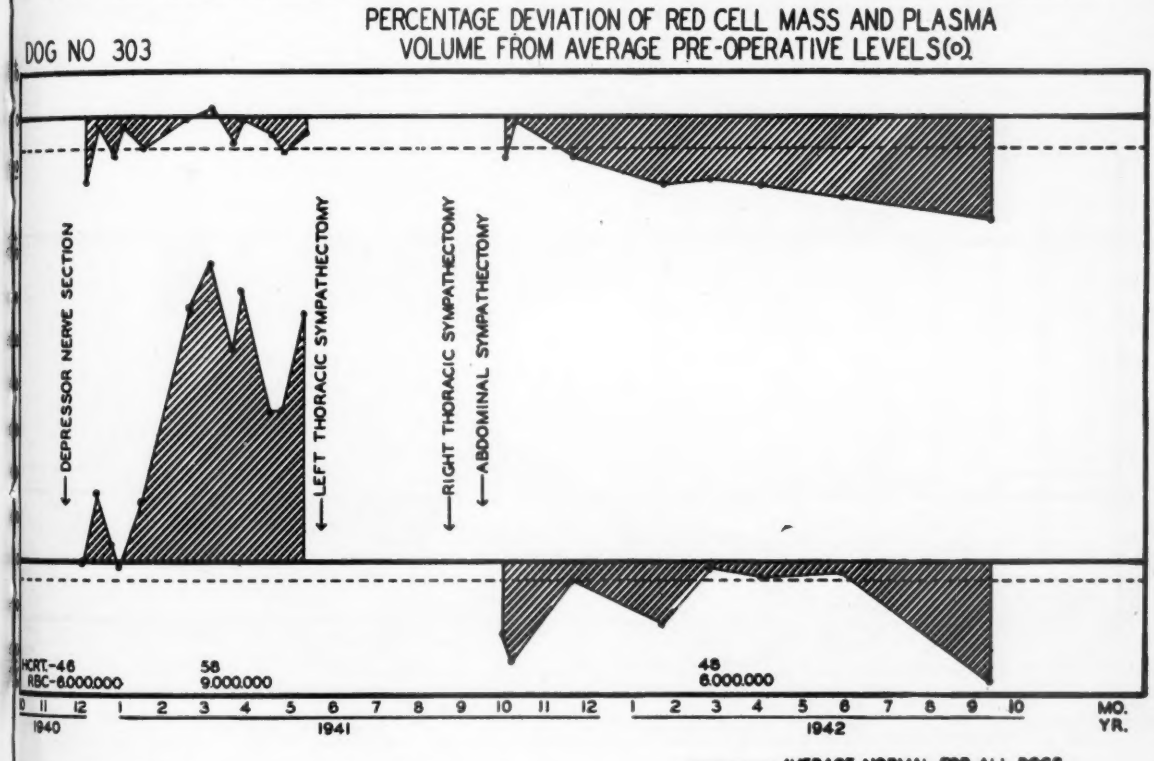


FIG. 8.—Changes in total body water observed following proprioceptor depressor neurotomy and extensive paravertebral sympathectomy expressed as percentage deviation from the average preoperative level (O) for each animal. The dogs are identified by the numbers at the bottom of the chart. The average over all change for each group is indicated by the large numbers above the horizontal line.

Since significant absolute changes in red cell mass had occurred in opposite directions in the diametrically opposite states of vasoconstriction and vasodilatation, interest was aroused as to the nature of this relationship which had been observed, and an experiment was devised to further explore this problem. Since we had at our disposal animals with chronic peripheral vasoconstriction and marked polycythemia which had apparently resulted from proprioceptor depressor neurotomy, the next obvious step was to perform extensive paravertebral sympathectomy upon these animals in an attempt to abolish the chronic peripheral vasoconstriction and then observe the body fluid changes which might occur. Polycythemic animals Nos. 303 and 309 were selected for this experiment, and the results observed are recorded in Table 4 and Figures 9 and 10. Although we had not observed polycythemia in all of the animals subjected to proprioceptor depressor neurotomy, 40 per cent of them had been so affected, and it was felt that some information of value might be obtained by subjecting the already sympathectomized animals to proprioceptor depressor neurotomy and observing the body fluid changes that might occur following this secondary operation. Nonpolycythemic animals Nos. 220 and 326 were selected for this experiment and the results observed are recorded in Table 4 and Figures 11 and 12. No significant alteration in plasma volume, red cell mass, total blood volume, red blood cell count or hematocrit was observed in Dogs Nos. 220 and 326 following proprioceptor depressor neurectomy. That the proprioceptor depressor neurectomy was actually accomplished is indicated by the fact that the mean arterial blood pressure of Dog. No. 220 increased from 107 mm. of Hg. postsympathectomy to 184 mm. of Hg. following proprioceptor depressor neurotomy, a 30 per cent increase over the dog's normal pressure of 134 mm. of Hg. The blood pressure of Dog. No. 326 increased from 122 mm. of Hg. postsympathectomy to 166 mm. of Hg. following proprioceptor depressor neurotomy, an 18 per cent increase over this dog's normal pressure of 141 mm. of Hg.



4.—Fluctuations in red cell mass, plasma volume, red blood cell count and hematocrit during a two-year period of observation of Dog 309 which was first subjected to proprioceptor depressor neurotomy and later to total paravertebral sympathectomy.



4a.—Fluctuations in red cell mass, plasma volume, red blood cell count and hematocrit during a two-year period of observation of Dog 303 which was first subjected to proprioceptor depressor neurotomy and later to total paravertebral sympathectomy.

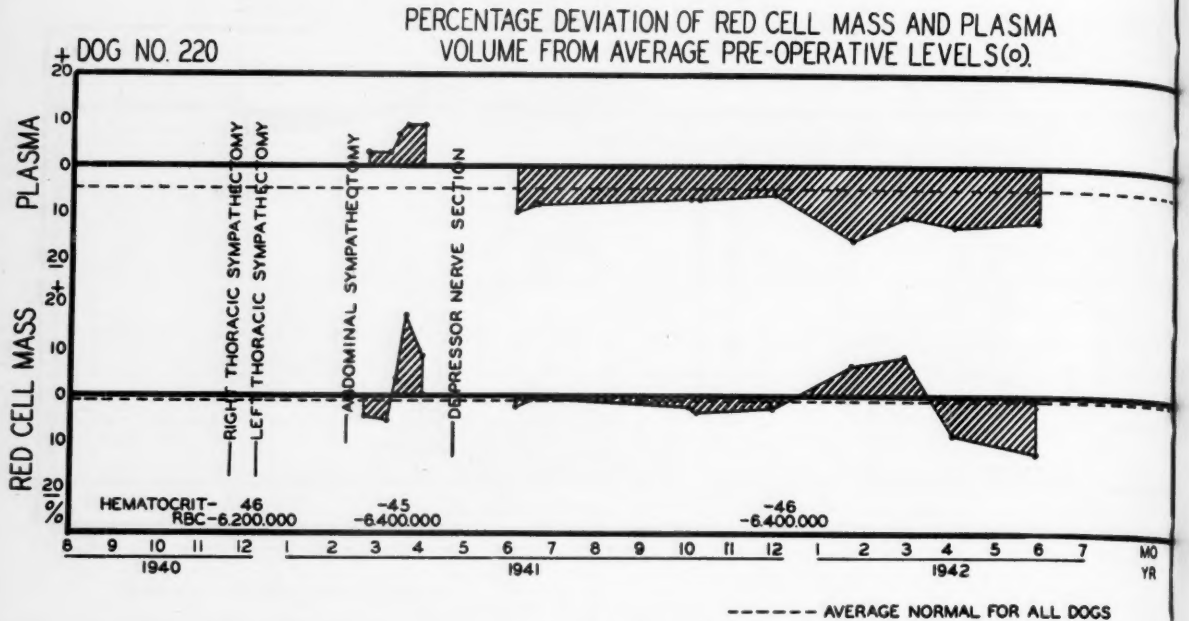


FIG. 11.—Fluctuations in red cell mass, plasma volume, red blood cell count and hematocrit during a two-year period of observation. Dog 220 which was first subjected to total paravertebral sympathectomy and later to proprioceptor depressor neurotomy.

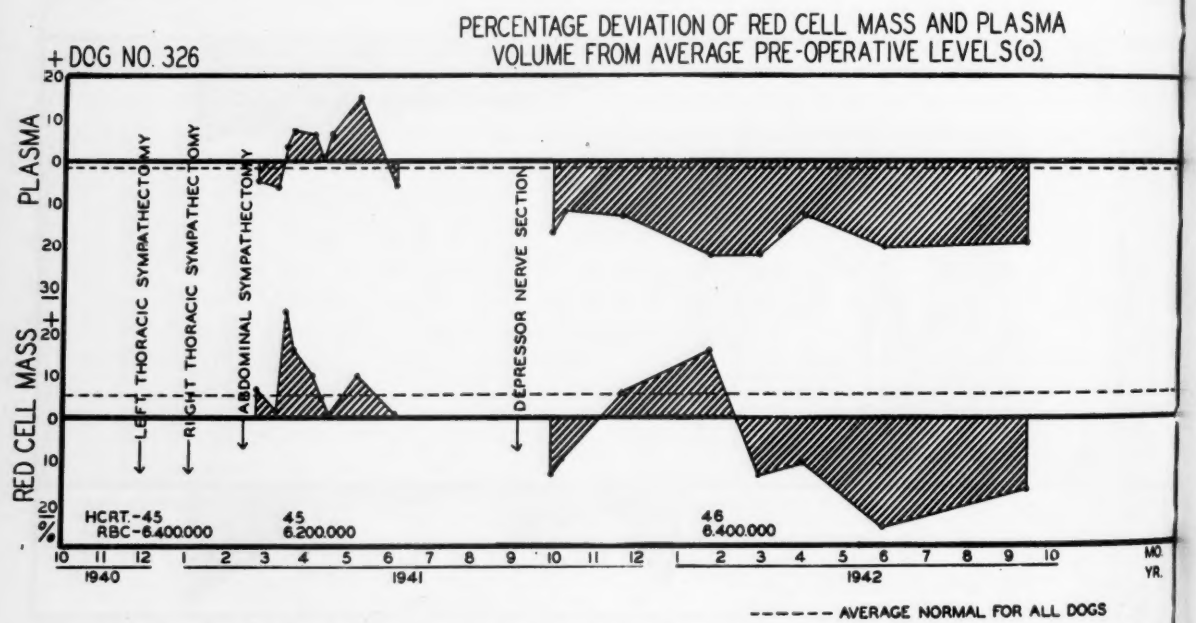


FIG. 12.—Fluctuations in red cell mass, plasma volume, red blood cell count and hematocrit during a two-year period of observation. Dog 326 which was first subjected to total paravertebral sympathectomy and later to proprioceptor depressor neurotomy.

Before any surgery had been done, Dog No. 309 had an average plasma volume of 445 cc., red cell mass of 372 cc., total blood volume of 817 cc., hematocrit of 45 per cent and a red blood cell count of 6,000,000, with an average mean arterial blood pressure of 138 mm. of Hg. This dog was an 11-Kg. male of heavy build, so that in both plasma volume and red cell mass its average preoperative values expressed in terms of cubic centimeters/kilograms of body weight were somewhat lower than the average determined for the entire group of animals. In Figure 9, the average plasma volume and red

TABLE IV

Changes in blood pressure and body fluids of four dogs subjected to both proprioceptor depressor neurotomy and extensive paravertebral sympathectomy. Dogs 303 and 309 were first subjected to proprioceptor depressor neurotomy and then to extensive paravertebral sympathectomy while Dogs 220 and 326 were operated upon in reverse order.

DOG NO.			303	309	AVERAGE			220	326	AVERAGE
DURATION OF OBSERVATION (months)	PRE-OP		1	2				3	2	
	AFTER PIN		6	6		AFTER SYM		2	4	
	AFTER SYM		12	12		AFTER PIN		12	12	
BLOOD PRESSURE (mm. Hg)	PRE-OP		138	138				134	141	
	AFTER PIN	Total	279	198		AFTER SYM	Total	107	122	
		% Change	+102	+45	+72		% Change	-20	-15	-16
	AFTER SYM	Total	189	220		AFTER PIN	Total	166	184	
		% Change	+37	+59	+48		% Change	+24	+30	+27
PLASMA VOLUME (cc.)	PRE-OP		596	445				616	676	
	AFTER PIN	Total	580	460		AFTER SYM	Total	670	720	
		% Change	-3	+2	0		% Change	+9	+6	+7
	AFTER SYM	Total	518	454		AFTER PIN	Total	556	557	
		% Change	-13	+2	-4		% Change	-10	-18	-14
RED CELL MASS (cc.)	PRE-OP		502	372				502	554	
	AFTER PIN	Total	760	540		AFTER SYM	Total	550	610	
		% Change	+51	+45	+48		% Change	+9	+10	+9
	AFTER SYM	Total	445	424		AFTER PIN	Total	478	515	
		% Change	-11	+13	+1		% Change	-5	-8	-6
TOTAL BLOOD VOLUME (cc.)	PRE-OP		1098	817				1118	1250	
	AFTER PIN	Total	1340	1000		AFTER SYM	Total	1220	1350	
		% Change	+22	+22	+22		% Change	+9	+8	+8
	AFTER SYM	Total	965	878		AFTER PIN	Total	1054	1070	
		% Change	-12	+8	-2		% Change	-8	-15	-10
"AVAILABLE" FLUID (cc.)	PRE-OP		2945	2088				2910	3365	
	AFTER PIN	Total	3420	2650		AFTER SYM	Total	3200	3750	
		% Change	+16	+27	+21		% Change	+10	+11	+10
	AFTER SYM	Total	3175	2650		AFTER PIN	Total	3140	3885	
		% Change	+8	+27	+17		% Change	+8	+15	+11
TOTAL BODY WATER (cc.)	PRE-OP		7059	5296				7005	8244	
	AFTER PIN	Total	6550	5600		AFTER SYM	Total	7000	7900	
		% Change	-7	+6	0		% Change	0	-4	-2
	AFTER SYM	Total	6581	5608		AFTER PIN	Total	6625	7842	
		% Change	-6	+6	0		% Change	-5	-5	-5

PIN - PROPRIOCEPTOR DEPRESSOR NEURECTOMY
SYM - PARAVERTEBRAL SYMPATHECTOMY

cell mass for the entire group is indicated by a dotted line showing that this animal's plasma volume was 6 per cent lower than the group average, and its red cell mass was 15 per cent lower than the group average. Proprioceptor depressor neurotomy was carried out in November, 1940, and the animal studied for a period of six months. By this time the red blood cell count had increased to 8,000,000, the hematocrit to 55 per cent, the plasma volume remained unchanged but the red cell mass had increased 45 per cent and the total blood volume 22 per cent. The blood pressure then averaged 198 mm. of Hg., a 43 per cent increase over the preoperative level. This animal was then subjected to a complete paravertebral sympathectomy in three stages, as described above, the last stage being performed in September, 1941. The animal was then studied for an additional year, during which time the red blood cell count returned to 6,000,000, the hematocrit to 48 per cent and the plasma volume, red cell mass and total blood volume all gradually returned to the preoperative level.

Before surgery, Dog No. 303 had an average plasma volume of 596 cc., red cell mass of 502 cc., total blood volume of 1,098 cc., hematocrit of 46 per cent, red blood cell count of 6,000,000, and an average mean arterial blood pressure of 138 mm. of Hg. In Figure 10, it may be seen that this 12.3-Kg. male animal's plasma volume was 7 per cent lower than the group average, and its red cell mass was 4 per cent higher than the group average. Proprioceptor depressor neurotomy was carried out in November, 1940, and the animal studied for a six-months period. By this time the red blood cell count had increased to 9,000,000, the hematocrit to 58 per cent, the plasma volume remained unchanged but the red cell mass had increased 50 per cent and the total blood volume, 22 per cent. The mean arterial blood pressure then averaged 279 mm. of Hg., a 102 per cent increase over the preoperative level. This animal was then subjected to a complete paravertebral sympathectomy in three stages, as described above, the last stage being done in September, 1941. The animal was then studied for an additional year, during which time the red blood cell count returned to 6,000,000, the hematocrit to 48 per cent, and the plasma volume, red cell mass and total blood volume all fell to slightly below the preoperative level.

The changes in "available fluid" and total body water recorded in Table 4 were not considered to be of significant magnitude.

DISCUSSION AND FURTHER CONCLUSIONS

From these data it became apparent that the polycythemia which had been observed to follow proprioceptor depressor neurotomy disappeared completely after complete paravertebral sympathectomy and that proprioceptor depressor neurotomy was not followed by the development of polycythemia in two animals which had previously had a complete paravertebral sympathectomy. Further, the severe hypertension which follows proprioceptor depressor neurotomy was greatly diminished by complete paravertebral sympathectomy and proprioceptor depressor neurotomy caused only a moderate hypertension in two animals which had previously had a complete paravertebral sympathectomy.

The inescapable result of study of these foregoing observations was to relate positively the autonomic nervous system to the peripheral red cell mass. Proof of the exact nature of this relationship is not available in these data but they do have certain general implications. First, polycythemia was never observed to occur spontaneously in any of the 29 dogs included in this experiment. Of the animals subjected to surgery, the sympathectomized animals never developed polycythemia and four of the six sympathectomized animals had decreases in red cell mass to lower levels than were recorded for any other dogs in the series. Forty per cent of the dogs subjected to proprioceptor depressor neurotomy developed polycythemia, characterized by absolute increase in the red cell mass to levels far higher than were observed to occur in any other dogs in the series. Polycythemic animals subsequently subjected to sympathectomy lost their polycythemia and non-polycythemic sympathectomized animals subjected to proprioceptor depressor neurotomy did not become polycythemic even though they did become mildly hypertensive. Thus, polycythemia occurred only in animals which had intact sympathetic efferent tracts with absence of afferent depressor pathways. We considered loss of the afferent depressor mechanism to be the stimulus for the development of the polycythemia and the efferent sympathetic depressor pathways to be the route over which this stimulus exerted its effect, namely, through vasoconstriction. The finding in these proprioceptor depressor neurotomized animals of a polycythemia characterized by increase in red cell mass and in total blood volume, such as is seen in polycythemia rubra vera in man, led us to consider the rôle of vasoconstriction in this latter condition.

EFFECT OF EXTENSIVE PARAVERTEBRAL SYMPATHECTOMY ON POLYCYTHEMIA RUBRA IN MAN

A direct approach to this problem was possible since extensive sympathectomy has long been used as a treatment for essential hypertension in the human and the safety of the procedure has been well-established. Dr. K. S. Grimson was at that time performing complete paravertebral sympathectomy in this clinic for the treatment of human essential hypertension, and his results have since been published.[19] He agreed to carry out this procedure upon a selected case of human polycythemia rubra vera. The background for this experiment is obvious from the foregoing data, the experiment resting on the premise that if polycythemia rubra vera in man is similar to the polycythemia of proprioceptor depressor neurotomy in dogs, then ablation of the sympathetic efferent pathways should cause the polycythemia to disappear.

Case Report.—The patient chosen for this critical test was a 27-year-old male laborer, who was first seen in this clinic in May, 1941. At that time, he complained of extreme fatigue, shortness of breath and severe headaches, and stated that he had had "polycythemia vera" for three years. He had apparently been well until the early part of 1938, when he noticed that he began to tire easily and by midyear was forced to quit his work as a laborer. By this time, he had become short of breath and was severely troubled by persistent headaches. It had been noticed that his complexion had become quite florid. He consulted his local physician who made a blood count and diagnosed his condition as polycythemia rubra vera and recommended that the patient go to a nearby

clinic for treatment. The patient complied with his local physician's recommendations, and was thoroughly studied at the designated clinic, the work-up including blue dye determination of the plasma volume and the red cell mass. The diagnosis of polycythemia rubra vera was confirmed, and a program of venesection begun. From late in 1938 until his first visit here, two and one-half years later, the patient had been bled from 600 to 1,000 cc. of blood on the average of every two weeks. For the first week following bleeding he would have considerable remission in his symptoms but the following week all would rapidly return with as marked severity as before. As a result, he was confined to bed about half of the time and was not able to work.

The family history revealed that his mother and father, age 65 and 70, respectively, were alive and well, as were also four sisters and one brother. No family history of disease could be elicited. He had been married for nine years, and his wife, age 25, was in good health. He was the father of four girls and one boy, age 8, 6, 5, 4, and 2 years. One child had died at birth. He stated that he had scarlet fever at the age of 14, complicated by mastoiditis. This had left him with a left facial palsy. He had undergone tonsillectomy in 1933, and appendicectomy in 1937. System inquiry added only the facts that he had recently developed a rather severe pain over the left anterior chest, which seemed to be relieved by bleeding, and that his memory had recently become markedly impaired.

Physical examination revealed the patient to be a well-developed and well-nourished man, weighing 70 kilograms. His temperature was 98° F.; pulse 68; respiration 16; and blood pressure 170/108 mm. of Hg. His face and hands were dull red in color. He was unable to hear a watch on his left side with the Weber test lateralized to the left and bone conduction greater than air conduction on the left. He had a complete left facial palsy to which he seemed well adjusted. Many dental caries were present and the pharynx was inflamed. Examination of the heart and lungs revealed no abnormality and aside from the scar of his previous appendicectomy, examination of the abdomen revealed similar normal findings. The liver was not enlarged, and it was debatable whether the lower pole of the spleen could be palpated. The extremities presented no clubbing of the fingers or other abnormality. No lymphadenopathy was present. Rectal examination was not remarkable and neurologic examination revealed only normal findings, aside from the left facial paralysis. His urine was found to be acid in reaction with a specific gravity of 1.025, negative for albumin and sugar, and with a normal sediment. White blood cell count was 11,000, with 67 per cent polymorphonuclear neutrophils, 26 per cent small lymphocytes, three per cent monocytes and three per cent eosinophils. Red blood cell count was 5,790,000, and hemoglobin 14.0 Gm./100 cc., with slight polychromasia, anisocytosis and poikylocytosis. Reticulocytes were 0.6 per cent. The diagnosis of polycythemia rubra vera was made and the patient entered the hospital on the Hematology Service, May 20, 1941, for further study. T-1824 dye dilution measurement of the blood volume was carried out, at which time the following results were obtained: Weight 71.5 Kg. Total blood volume, 6,120 cc. Plasma volume 2,907 cc. Hematocrit 53 per cent. Total red cell mass, 3,212 cc. (51.9 cc. Kg. of body weight).

The patient remained in the hospital for two weeks, during which time his red blood count increased to 6,890,000 and his hemoglobin to 16.0 Gm./100 cc. His face became more deeply dull red in color and he began to develop a tight substernal sensation, and his headaches continued. Since the response of this patient to venesection had been poor it was elected to try roentgenotherapy to his long and flat bones. Between June 3, 1941, and July 24, 1941, he received eight treatments of 160 r in air each, directed to both femora, scapulae, anterior ribs and iliac blades. He received slight subjective relief following this therapy but on return to the clinic, December 15, 1941, he presented the same picture as before having received this therapy, and at that time his red blood cell count was 6,500,000 and his hemoglobin 16.7 Gm./100 cc. He again entered the hospital, December 20, 1941, for further observation. The eye consultants reported that his fundi showed bilateral papilledema with blurring and hyperemia of both disks. The veins

appeared fuller and more deeply red than usual. The arteries showed slight tortuosity and only slight increase in light reflex. A few focal spasms were present but crossing signs were not observed. The A-V ratio was 2:4 and no hemorrhages or exudates were present. They felt that the patient exhibited slight early hypertensive vessel changes and that the ocular fundus picture was compatible with a diagnosis of polycythemia rubra vera. The renal vascular disease consultants concurred in the diagnosis of very mild hypertension but did not believe that this hypertension was the basis for the patient's symptoms. They felt that the ocular fundus changes were due to increased intracranial pressure referrable to the polycythemia and that the polycythemia was responsible for all of the patient's symptoms. The decision was then made to subject this patient to sympathectomy, not with the idea of treating his very mild asymptomatic hypertension but to see what effect sympathectomy would have on the course of his polycythemia.

Accordingly, January 9, 1942, a left paravertebral sympathectomy was performed, and on January 29, 1942, the same procedure was carried out on the right side. The operation was identical with that described for the animals used in this experiment, and has been elsewhere described by Grimson.[20] The extent of resection can be appreciated from study of the specimen removed at the first operation (Fig. 13). It included the left ganglionated sympathetic trunk from T-1 through L-2, together with the stellate and a portion of the celiac ganglia and all of the left splanchnic nerves. The amount of blood lost during these operative procedures was measured and the patient transfused with whole blood slightly in excess of the amount lost. At no time was venesection done. Careful studies of his blood volume and blood composition have been made repeatedly since the patient's first hospitalization here and are summarized in Chart 5 and Figures 14 and 15. The patient was discharged from the hospital, March 1, 1942, to be readmitted five, 23 and 39 months following operation for reëvaluation of his status on each of these occasions. The last study was made in April, 1945. These data are, likewise, recorded in Chart 5 and Figures 14 and 15. At no time has a significant change been noted in his plasma volume. However, immediately following surgery, his total blood volume and red cell mass fell abruptly and then gradually increased, so that two years following operation the preoperative level had again been reached. His red blood cell count, hemoglobin and hematocrit changes have paralleled the change in total blood volume and red cell mass.

In spite of the fact that there has been a return of his blood picture to that of mild polycythemia, this patient has been completely relieved of all of his symptoms, and only in the past few months has he had any difficulty. He now notices that after long hours at work he develops a headache but he volunteers the information that this is not similar to, nor is it as severe as the headaches he had before his operation. He is now employed as an hospital orderly in his home town, and works strenuously 14 hours a day. At no time since his operations in January 1942 has he been bled, nor has he been subjected to any form of medicinal therapy for his polycythemia, and he now considers himself to be a well individual.

Discussion.—In evaluating the results of extensive paravertebral sympathectomy in this case of human polycythemia rubra vera, one must be cautious, since spontaneous remission is known to occur in this disease. It was for this reason that this case was not reported at any earlier date. We have now had an opportunity to observe this patient for a period of more than three years since surgery was performed, and certain valid statements are now possible. First, there can be no question about the fact that the function of this man's peripheral constrictor mechanism was greatly reduced if not abolished by surgery. Evidence for this is the marked postural hypotension which he developed. As late as two months after his second stage syncope would occur if he abruptly changed from the lying to the standing

position, and it was not until five months after operation that this side-effect of the operation ceased to be a troublesome complication. The starch-iodine sweat tests illustrated in Figure 15, also indicate the extensive interruption of efferent sympathetic pathways that was brought about. Also, one would not question the fact that the blood volume and blood composition were

TABLE V

Effect of extensive paravertebral sympathectomy on the plasma volume, red cell mass, total blood volume, red blood cell count and hemoglobin of the case herein described.

DATE	TOTAL BLOOD VOLUME	RED CELL MASS	PLASMA VOLUME	HEMATOCRIT	RBC	Hb
12/22/41	6120	3212	2908	53	6,400,000	16.7
1/5/42	5821	3085	2736	53		
1/9/42	5350	2889	2461	54		
1/9/42	LEFT THORACIC SYMPATHECTOMY					
1/16/42	4800	2163	2637	45	4,910,000	14.7
1/25/42	5250	2430	2820	46		
1/29/42	RIGHT THORACIC SYMPATHECTOMY					
2/5/42	5150	2270	2880	44	5,270,000	15.3
2/21/42	4400	1940	2460	44		
6/6/42	5100	2680	2420	52	6,310,000	17.6
6/11/42	5040	2620	2420	52		
12/13/43	5500	3130	2370	57	5,790,000	18.0
3/30/45	5540	3160	2380	57	6,240,000	19.8
4/4/45	5500	3197	2303	58		

other than normal as late as two months following operation, in spite of the fact that a careful measurement and estimation of the blood loss attendant with his operative and postoperative period were made and that this loss was replaced by transfusions of whole blood. Lastly, one must accept the fact that this patient has remained asymptomatic and has become capable of strenuous prolonged labor without resort to any form of treatment for his disease. The fact still remains, however, that in the first two years following operation there was a gradual elevation of his blood volume and blood composition to levels not dissimilar to those observed before operation, but in

the third postoperative year only slight further increases were recorded. Further, this recurrence of polycythemia has not been attended by recurrence of subjective symptoms, nor has it in any way incapacitated the man, or required further therapy.

It was obvious to us that some of the above observations had to be further explored if a positive relationship between peripheral vasoconstriction and

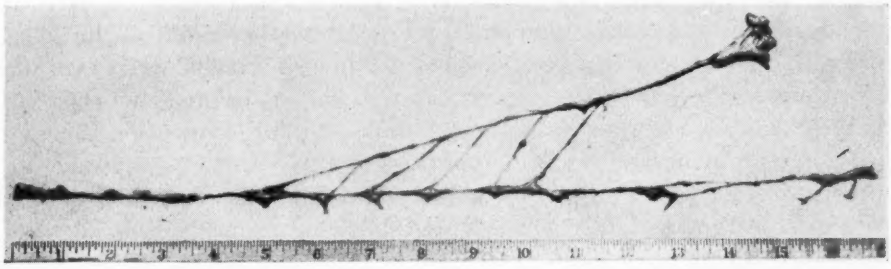


FIG. 13.—Photograph of a specimen obtained at the time of the first operation on the patient herein described. At the left is the left stellate ganglion and at the upper right, a major part of the left coeliac ganglion. At the bottom right are the first and second lumbar ganglia of the sympathetic trunk. The remainder of the specimen consists of the left ganglionated sympathetic trunk and splanchnic nerves.

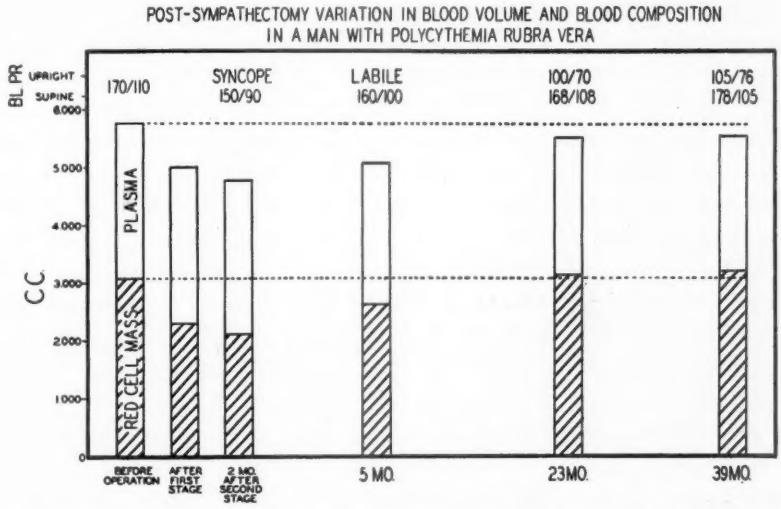


FIG. 14.—Correlation of the postsympathectomy alterations in blood volume and blood composition and supine and upright blood pressures observed in the patient herein described.

polycythemia was to be maintained. In the experimental animals, polycythemia required intact sympathetic efferent fibers for its existence, yet, in this patient asymptomatic polycythemia had recurred following extensive paravertebral sympathectomy. From our experience, with both dogs and man, we knew that maintenance of complete interruption of sympathetic efferent pathways was not possible. Thus, while complete paravertebral sympathectomy actually destroys these pathways and results in vasodilatation, the effect is not permanent, and a gradual restoration of sympathetic control develops. We routinely find profuse proliferation of nerve fibers through the scar of the extrapleural space when autopsy examination of pre-

viously sympathectomized animals is carried out remote from the time of operation. Further, dogs which have been previously sympathectomized are not completely protected from the development of hypertension when subsequently subjected to proprioceptor depressor neurotomy, although the hypertension which does develop is always slight or moderate as compared to the hypertension which follows proprioceptor depressor neurotomy in the normal dog. Again, although the hypertension which follows proprioceptor depressor neurotomy disappears, or is greatly diminished, following extensive paravertebral sympathectomy, there is a gradual return of the blood pressure to high levels, though never so high as before sympathectomy in these animals. In man, postsympathectomy postural hypotension is always most severe immediately after operation, and it becomes gradually and progressively less marked as time goes by, but is usually demonstrable even late after surgery. Lastly, immediately following sympathectomy in man, sweating does not occur in the denervated areas of skin, but there is a gradual and progressive recovery of this function. This phenomenon can be most easily recorded by the use of starch-iodine sweat tests. As part of the study of the above-described case, frequent lying, sitting and standing blood pressure readings were made on each hospital admission as well as starch-iodine sweat tests. These data are summarized in Figures 14 and 15. The average of all preoperative blood pressure readings on this man was 170/110 mm. of Hg., with no demonstrable evidence of postural effect.

Each blood pressure reading recorded in Figure 14 represents the average of all designated readings made during each hospital stay. As late as two months after his second stage his blood pressure could not be obtained in the upright position. By five months, it was extremely labile and at very low levels. At 23 months after operation, his average standing pressure was 100/70 mm. of Hg. and at 39 months, 105/76 mm. of Hg. The average supine blood pressure readings, likewise, show a gradual return to approximately the preoperative levels. A closely parallel change was observed in this patient's sweating function, and is pictorially presented in Figure 15. Here one observes the gradual and progressive increase in both the area of skin in which sweating occurs and in the amount of sweating which occurs in these areas. The decrease in postural hypotension, return of supine blood pressure level, and the increase in sweating ability were interpreted to mean recovery of sympathetic efferent function in this man, presumably mediated through regeneration of sympathetic efferent fibers. As may be seen from Figures 14 and 15, these changes parallel exactly the observed changes in blood volume and blood composition. Thus, the recurrence of the polycythemia, when viewed in conjunction with these observations on sympathetic efferent phenomena, serve not to disprove the positive relationship between vasoconstriction and polycythemia but to further support this view.

Much investigative work will have to be done before the implications of this report can become firmly established, yet one cannot but be impressed by the likelihood of autonomic nervous system control of certain functions of the bone marrow. This study has been conducted by alteration of this rela-

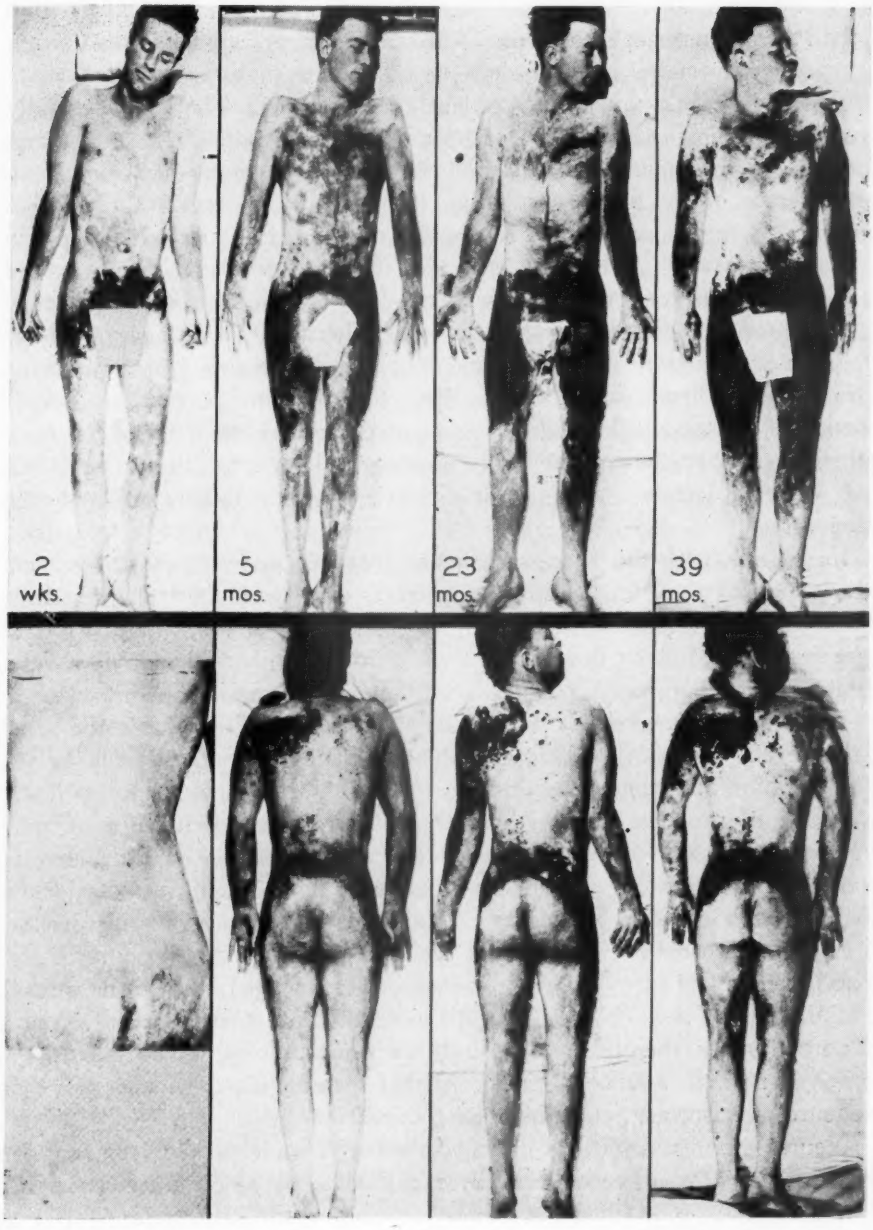


FIG. 15.—Starch-iodine sweat tests at one-half, five, twenty-three and thirty-nine months following extensive paravertebral sympathectomy in the patient herein described. Progressive recovery of his sweating function is seen.

tionship remote from the zone of ultimate effect, the bone marrow, and the results obtained have been the observed changes in an equally remote area, the peripheral blood. Yet, all of our observations lead us to the impression that the sympathetic efferent fibers do control erythropoiesis and, to us, the most likely basis for this control lies in the state of vasoconstriction or vasodilatation of the presinusoidal vessels of the bone marrow. We know from

countless observations that any condition characterized by lack of oxygenation of the systemic arterial blood will, likewise, present polycythemia as a result of hyperactivity of the myeloid elements of the marrow, presumably due to the presence of the unoxygenated blood in the marrow. The most generally accepted and most plausible theory of normal production of the red cell is that there is intermittent constriction and dilatation of vessels leading to the sinusoids of the marrow and that during states of presinusoidal vasoconstriction, the blood of the sinusoids so affected is isolated from the general circulation. Low oxygen tension develops in these sinusoids and acts as a stimulus for red cell production. It is our impression that the tone of these presinusoidal blood vessels is under the control of the sympathetic efferent nerves in states of health and that the fundamental defect in many cases of polycythemia rubra vera is likely to be a more persistent vasoconstriction of presinusoidal blood vessels as a result of overactivity of the sympathetic nerves to these vessels. Supporting evidence for this view is the study of blood lactate levels following exercise in patients with polycythemia rubra vera.[21]

In patients with this disease, whether they are under treatment or not, exercise causes a fall in blood lactate whereas exercise in normal individuals is followed by a rise in blood lactate. A possible explanation for this is that there is decreased blood flow through the tissues in polycythemia rubra vera, resulting in an high resting blood lactate and an accumulation of lactate in the tissues, so that exercise with vasodilatation would cause a fall in the blood lactate level. The work of Davis in the production of polycythemia by the administration of various vasoconstrictor drugs indicates that vasoconstriction is capable of producing polycythemia.[22] The frequent occurrence of mild hypertension in polycythemia rubra vera has generally been attributed to increased blood viscosity or has been regarded as being due to the coincidental existence of essential hypertension. In a series of 163 cases of this disease, Tinney has reported a systolic blood pressure of more than 150 mm. of Hg. in 40 per cent, and of more than 180 mm. of Hg. in 9 per cent of the cases.[23] It has frequently been observed that the blood pressure does not always return to normal after therapeutic measures have caused the blood picture to approach normal levels. This is further presumptive evidence for the existence of vasoconstriction in these individuals.

Neurologic manifestations in polycythemia rubra vera are very common and intracranial lesions are generally regarded to be of common occurrence in this disease. The almost universal attitude toward this relation is that the nervous system lesion is always secondary to the polycythemia. Our experimental neurogenic polycythemia described above was produced by section of afferent cervical depressor pathways, the carotid sinus and cardioaortic nerves, which caused uninhibited activity of vasoconstrictor impulses over the efferent sympathetic mechanism. Although the point of origin of the imbalance of this mechanism in our experiments was at the level of the afferent depressor mechanism, it is conceivable that there could be conditions in which the central nervous system portion of this reflex arc could be

influenced either directly by mechanical, inflammatory or neoplastic disease or indirectly through connections with other areas of the central nervous system. Experimentally, only meager efforts have been made to produce polycythemia by manipulations in the region of the diencephalon and the results of this work are not convincing.[24, 25] The report of Carpenter, *et al.*,[26] of two cases of hemangioblastoma of the cerebellum with associated absolute polycythemia, which in each case disappeared following extirpation of the tumor could well represent instances of mechanical stimulation of the central connection of this reflex arc which is here under study. It is of interest that one of these cases presented with a blood pressure of 160/120 mm. of Hg. and that this moderate hypertension disappeared after operation. Another similar case has more recently been reported by Walker.[27] A rather substantial volume of clinical literature has accumulated in the past two decades causally relating polycythemia to primary lesions of the brain stem, but these reports are so incomplete, either from the standpoint of accurate diagnosis or inadequacy of anatomic and pathologic verification of findings, that they serve to confuse rather than clarify the problem. This literature has been adequately reviewed by Da Rin and Costa,[28] Ferraro and Sherwood,[29] and Lucia and Marasse,[30] and will not here be repeated.

SUMMARY

1. Using dilution methods, the following average normal values were observed in 29 normal dogs: Plasma volumes 54 cc. Kg. of body weight. Red cell mass, 47 cc. Kg. of body weight. Total blood volume 101 cc. Kg. of body weight. "Available fluid," 279 cc. Kg. of body weight. Total body water, 640 cc. Kg. of body weight.

2. Following proprioceptor depressor neurotomy six of 13 animals developed absolute polycythemia and all became hypertensive.

3. Following extensive paravertebral sympathectomy, four of six animals developed a significant decrease in red cell mass and total blood volume.

4. Two dogs with chronic peripheral vasoconstriction which had resulted in persistent marked hypertension and persistent marked absolute polycythemia were subjected to extensive paravertebral sympathectomy which resulted in decrease in the blood pressure to moderate hypertensive levels and disappearance of the polycythemia.

5. Two dogs with chronic peripheral vasodilatation, which had resulted in transient minimal hypotension, were subjected to proprioceptor depressor neurotomy, which resulted in the gradual appearance of a moderate hypertension but polycythemia was not observed to occur.

6. The case of a 27-year-old man with intractable polycythemia rubra vera is presented, and the effect of extensive paravertebral sympathectomy recorded. Thirty-nine months after operation he is asymptomatic, without further therapy, and is able to perform prolonged strenuous labor. The postoperative change in his blood volume and blood composition has been related to sympathetic efferent function.

7. The relationship of these data to the normal and abnormal physiology

of red blood cell formation by the bone marrow is discussed, and the meager experimental literature reviewed.

CONCLUSION

By means of proprioceptor depressor neurotomy a form of absolute polycythemia has been experimentally produced in dogs, and it has been shown that this form of experimental polycythemia disappears following extensive paravertebral sympathectomy. Support is given to the theory that the normal and some abnormal formation of red blood cells by the bone marrow is under the control of the sympathetic nervous system through its regulation of the caliber of the presinusoidal vessels of the marrow. The theory is advanced that some cases of polycythemia rubra vera in man are due to constriction of the presinusoidal blood vessels of the bone marrow and extensive paravertebral sympathectomy is proposed as treatment for this disease. The successful result of treatment of a man with polycythemia rubra vera by extensive paravertebral sympathectomy is recorded.

BIBLIOGRAPHY

1 Barron, A. G., and Barron, E. S. G.: Proc. Soc. Exp. Biol. and Med., **35**, 407, 1936.
2 Adams, W. E., Thornton, T. F., Jr., and Eichelberger, Lillian: Arch. Surg., **49**, 51, 1944.
3 Vaquez, H.: Compt. rend. Soc. de biol., **4**, 384, 1892.
4 *Idem:* Bull. et mém. Soc. méd. d'hôp. de Paris, **12**, 60, 1895.
5 Osler, W.: Am. J. M. Sc., **126**, 187, 1903.
6 *Idem:* Brit. M. J., **1**, 121, 1904.
7 Türk, W.: Wien. klin. Wchnschr., **15**, 163, 1902 and **15**, 372.
8 *Idem, ibid.:* **17**, 153, 1904.
9 Bernard, Claude: Compt. rend. Soc. de biol., **4**, 168, 1852.
10 Cyon, E. von, and Ludwig, Carl: Ber. Sächs. Ges., **18**, 307, 1866.
11 Bronk, D. W., Proc. Soc. Exp. Biol. and Med., **28**, 1014, 1931.
12 Hering, Heinrich Ewald: Die Karotissinusreflexe auf Herz und Gefasse vome normal-physiologischen und pathologisch-physiologischen und klinischen Standpunkt. **6**, 150. Dresden. T. Steinkopf, 1927.
13 Heymans, C., and Bouckaert, J. J.: Compt. rend. Soc. de biol., **106**, 471, 1931.
14 Schafer, P. W.: Proc. Soc. Exp. Biol. and Med., **49**, 327, 1942.
15 *Idem:* Surg., Gynec. & Obst., **79**, 163, 1944.
16 Gibson, J. G. 2nd, and Evans, W. A. Jr.: J. Clin. Invest., **16**, 301, 1937.
17 Crandall, L. A., Jr., and Anderson, M. X.: Am. J. Digest. Dis. and Nutrition, **1**, 126, 1934.
18 Painter, E. E.: Am. J. Physiol., **129**, 744, 1940.
19 Grimson, K. S.: Surg., Gynec. and Obst., Internat. Abstr. Surg., **75**, 421, 1942.
20 *Idem:* ANNALS OF SURGERY, **114**, 753, 1941.
21 Hallock, P.: Proc. Soc. Exp. Biol. and Med., **38**, 587, 1938.
22 Davis, J. E.: Am. J. Physiol., **134**, 219, 1941.
23 Tinney, W. S., Hall, B. E., and Giffin, H. Z.: Proc. Staff Meetings of the Mayo Clinic. **18**, 94, 1943.
24 Schulhof, K., and Mathies, M. M.: J. A. M. A., **89**, 2093, 1927.
25 Riccitelli, L.: Rivista di Patologia Nervosa e Mentale, **45**, 499, 1935.
26 Carpenter, G., Schwartz, H., and Walker, A. E.: Ann. Int. Med., **19**, 470, 1943.
27 Walker, A. E.: Society Transactions, Arch. Neurol. and Psychiatry, **53**, 251, 1945.
28 Da Rin, O., and Costa, L.: Clin. med. Ital., **65**, 303, 1934.
29 Ferraro, A., and Sherwood, N. D.: Psychiatric Quart., **11**, 19, 1937.
30 Lucia, S. P., and Marasse, H. F.: J. Nervous and Mental Diseases, **99**, 734, 1944.

PRINCIPLES AND PRACTICE OF PENICILLIN THERAPY IN DISEASES OF THE NERVOUS SYSTEM

A. Earl Walker, M.D., and Herbert C. Johnson, M.D.

Chicago, Ill.

FROM THE DIVISION OF NEUROLOGICAL SURGERY, UNIVERSITY OF CHICAGO, CHICAGO, ILLINOIS.

Penicillin is the most powerful chemotherapeutic agent now known, and its value in infections of the nervous system is well-recognized. However, its administration for optimal results in the treatment of nervous diseases is not yet standardized. This is, in part, due to the fact that most emphasis has been placed upon the antibiotic effect of the drug on the invading organism and little attention paid to its pharmacologic effect upon the brain and spinal cord, which are equally important factors in arriving at a rational therapeusis. In part, it is due to a lack of exact knowledge of the distribution and dispersion of the drug in the spinal fluid after systemic and intrathecal administration. The accumulated clinical experience in the use of penicillin augmented by fundamental studies of these factors should give a more rational basis for the therapy of diseases of the nervous system.

PENICILLIN SENSITIVITY OF THE ORGANISMS

In general, penicillin is effective against gram-positive aerobic or anaerobic organisms, and relatively innocuous to the gram-negative organisms. However, within the group of gram-positive organisms a wide range of sensitivity is found, and even strains of the same organism may exhibit variations in susceptibility to the antibiotic action of penicillin. For this reason it is essential to know not only the type of infecting organism but its penicillin sensitivity. Several tests, modifications of one of the methods of penicillin assay, have been suggested as a means of determining the relative susceptibility to penicillin of an organism.[8, 3] *In vitro* and *in vivo* experiments have demonstrated that at certain critical penicillin concentrations any given susceptible organism may be destroyed within a certain time. With lesser amounts of penicillin the organisms will grow indefinitely.[21] In the case of the *Streptococcus haemolyticus* doubling of this critical penicillin concentration roughly halves the time necessary for killing the organisms. But a still further greater concentration does not appreciably shorten the lethal period. From *in vitro* experiments the critical concentrations for the more common organisms found in infections of the central nervous system[21] have been determined (Table I.)

There is no reason to believe that these concentrations are not equally applicable to the spinal fluid. In general, then, one might conclude that a concentration of penicillin in the cerebrospinal fluid of 0.036 Oxford units/cc. for a period of at least three hours should be adequate to destroy *Streptococcus haemolyticus* organisms. However, two other factors must be considered.

In the first place, the number of organisms present in the meninges may be so great that the effectiveness of the penicillin is decreased. Probably more important is the fact that organisms may be introduced into the subarachnoid space from foci which are inaccessible to the drug. For this reason

TABLE I

CRITICAL CONCENTRATIONS FOR THE MORE COMMON ORGANISMS FOUND IN INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

Organism	Time Exposed	Concentration of Penicillin in Blood Units/Cc.
Streptococcus haemolyticus (*Meningococcus* approx. the same 1)	3 hrs.	0.036
Staphylococcus aureus	3 hrs.	0.066
Pneumococcus, Type I (Types III and VII approx. the same 1)	3 hrs.	0.078
Streptococcus viridans	3 hrs.	1.50

the theoretic exposure time necessary for killing is inadequate in practice. However, the effective concentrations for the various bacteria give an indication of the relative amount of penicillin necessary to control an infection due to that particular organism.

MODES OF ADMINISTERING PENICILLIN

Systemic Administration.—Although the earlier investigators[13, 10, 20] were unable to detect penicillin in the spinal fluid there is accumulating evidence that it may enter the spinal fluid and attain an adequate bacteriostatic concentration after parenteral administration.[4, 24] Under normal conditions of the meninges in experimental animals and man, penicillin has been detected in the spinal fluid in only a very small percentage of cases.[11] If the meninges were irritated by bacterial, chemical or physical agents, however, penicillin was found to pass through readily to the spinal fluid. Whereas, intravenous administration of sufficient penicillin to produce blood levels of 23.5–32.5 Oxford units per cc. did not cause any of the drug to be detected in the spinal fluid of the Macaque monkey, after inducing a meningeal reaction by cerebral concussion or by the intrathecal injection of air, heparinized blood or bacteria, from 0.17–0.78 Oxford units per cc. of penicillin were usually found in the spinal fluid. Occasionally concentrations as high as 10–50 per cent of a blood level of 10–25 units per cc. were found. In man penicillin given intramuscularly six to eight hours after pneumo-encephalography may be detected in the spinal fluid within an hour. In animals with meningitis the penicillin may be detected in the spinal fluid for as long as three hours after its systemic administration. Rammelkamp and Keefer[19] found that the absorption of the penicillin from the cerebrospinal fluid was more rapid in patients suffering from meningitis than in normal subjects.

On the basis of these studies it seems that a concentration of penicillin adequate for the more sensitive organisms may be maintained in the spinal fluid by systemic administration of the drug every three hours.

Intrathecal Administration.—Because a sufficiently high concentration to kill the bacteria more resistant to penicillin probably cannot be obtained by

systemic administration, supplemental intrathecal injection is necessary in some cases. The ideal route of intrathecal administration would be one by which the penicillin would be equally distributed in the subarachnoid space, with the highest concentration, if a gradient were present, about the foci of infection. An understanding of the dispersion and distribution of penicillin in the spinal fluid when given by lumbar, cisternal and intraventricular routes is essential to determine the optimum technic.

When the drug is injected into the lumbar subarachnoid space of man its dispersion throughout the spinal fluid is quite slow. Within one to two hours the drug can usually be detected in the cisternal fluid, reaching a peak concentration in two to six hours of 0.4 per cent/cc. of the amount injected. However, in some cases the penicillin is apparently absorbed before it can reach the cisterna magna, for in several instances in man no penicillin has been detected in the cisternal fluid after the lumbar injection of 20,000 Oxford units, and in one case after the injection of 30,000 Oxford units.[11] The concentration of the drug in the lumbar region rapidly falls, so that four hours after injection it is usually under 0.5 per cent/cc. of the amount injected. However, an adequate bacteriostatic concentration is maintained for approximately 24 hours (Chart 1).

When the drug is injected into the cisterna magna of man the concentration in the lumbar subarachnoid fluid rapidly increases so that two hours after the injection it is approximately 1 per cent/cc. of the amount given. In four hours it has decreased to one-half that concentration. After that time the concentration curves of the lumbar spinal fluid, following lumbar and cisternal injection of penicillin, are practically identical (Chart 2). In dogs the ventricular concentration after cisternal injection is higher than after lumbar injection. Presumably the concentration in the basal cisterns and subarachnoid space over the convexity of the brain is also higher.

Intraventricular injection of penicillin in man should be followed by rapid and widespread dispersion of the drug if it follows the pattern of diffusion of dyes injected intraventricularly. Because a perforation in the skull is necessary this mode of administration is undesirable as a routine method of giving penicillin.

From the standpoint of dispersion of the drug, the injection of penicillin into the cisterna magna is the best route available. However, cisternal puncture is not without danger, even in experienced hands, so that usually it is wise to sacrifice the somewhat better distribution of the drug, for the greater safety of lumbar injection.

DOSAGE

If an attempt is to be made to control the infection of the central nervous system by systemic administration, the penicillin must be given in relatively large amounts (40,000, or more, units) at three-hour intervals or continuously intravenously. If the condition does not respond to this dosage, intrathecal administration of the drug is desirable. In the usual case 10,000

Oxford units of penicillin dissolved in 5–10 cc. of distilled water or normal saline and injected intrathecally is quite sufficient to maintain an adequate bacteriostatic level in the spinal fluid for 24 hours. Larger amounts of penicillin may give rise to severe reactions.[19, 22] Injections at 12-hour intervals are likely to be accompanied by prolonged fever and signs of meningeal irritation.[22]

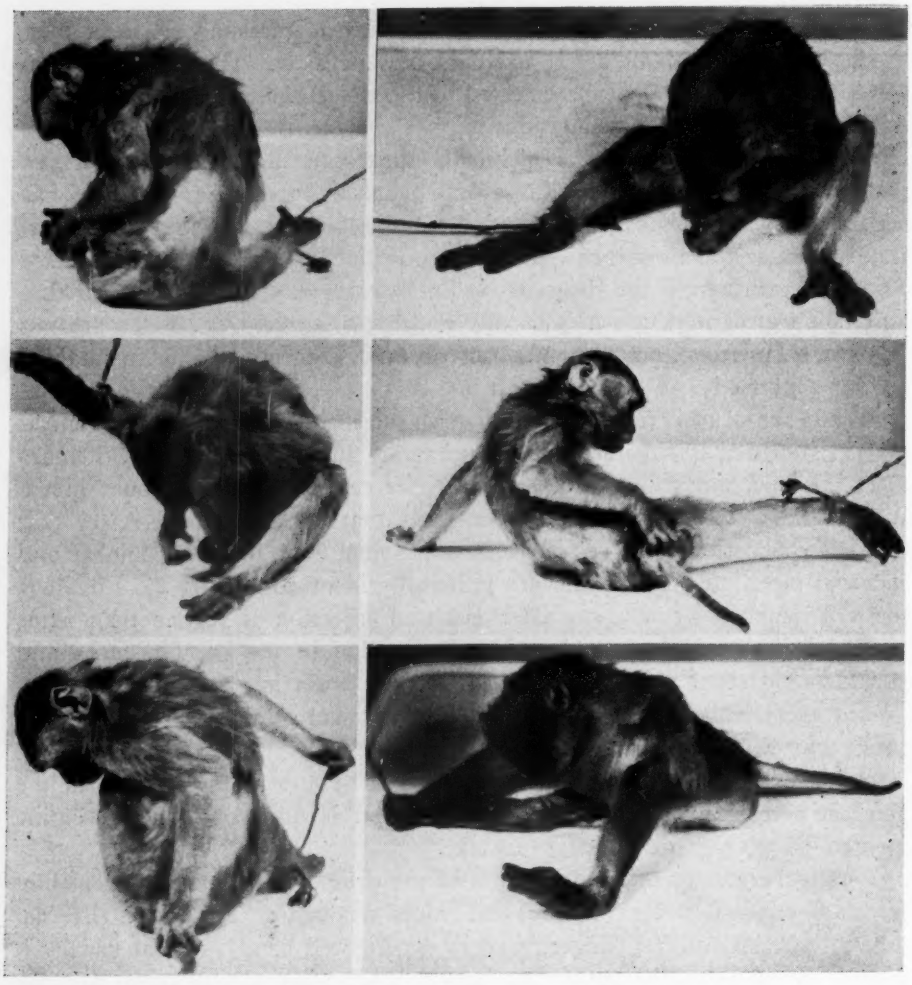


FIG. 1.—Photographs showing the reactions of a monkey ten minutes after injection of 20,000 Oxford units into the lumbar subarachnoid space. That the animal is experiencing peri-anal paresthesias seems evident.

REACTIONS TO INTRATHECAL INJECTION OF PENICILLIN

Fortunately, there is relatively little reaction of the meninges to the injection of penicillin.

Pleocytosis.—The more purified products now available cause only a slight pleocytosis, usually less than 100 cells, the majority of which are

lymphocytes, with or without a slight increase in protein. There appears to be some variation in amount of the impurities in the products manufactured by different companies. From the injection of some preparations a marked sterile meningitis is produced but this is rare at the present time. Usually there is no systemic reaction to amounts of 10,000 units or less.

Radiculitis.—Although relatively small doses produce the effects mentioned above, larger doses may cause serious and alarming sequelae. In monkeys 20,000 Oxford units in 1 cc. of normal saline, injected into the lumbar subarachnoid space has produced severe reactions[11] (Fig. 1). Within ten minutes of the injection, the animal would begin to inspect, rub, and then scratch vigorously his tail and peri-anal region. This behavior might persist for one-half to one hour. It seemed probable that the animal was experiencing paresthesias. Although the monkey appeared to be well the next day there is clinical evidence that such radicular reactions may not be so fleeting.

We have seen, in consultation, an adult male who, as a complication of a cholesteatomatous otitis media developed severe symptoms and signs of meningeal irritation. A radical mastoidectomy was performed. The spinal fluid the following day, although sterile, contained 3,000 cells. At this time 100,000 units of penicillin in 5 cc. of saline were given intrathecally. Twelve hours later the patient complained of urinary retention and paresthesias in the saddle region. A marked hypesthesia in this area was found. The urinary and sensory disturbance gradually decreased but when the patient attempted to walk two weeks after operation his legs were weak and unsteady. Over a period of three months the disturbance gradually cleared up. To complicate this case it was found that the patient had had a positive Wassermann reaction in the blood 12 years previously, although his spinal fluid reaction was negative. The patient neglected any antiluetic therapy and at the time of hospitalization for his above mentioned complaints his blood Wassermann reaction was still 4 plus. The spinal fluid Wassermann, however, was negative and the colloidal gold curve was normal.

It seems, therefore, that this case should be considered a sacral radiculitis resulting from penicillin therapy. That the systemic luetic infection was the main factor in the complication seems improbable. Similar reactions have been reported in individuals not suffering from syphilis.[26] In retrospect, the intrathecal penicillin therapy used in this patient seems rather severe because an actual infection of the meninges was never established and the patient's condition, general and local, did not appear to be severe enough to warrant the large dosage.

Arachnoiditis.—Occasionally a localized arachnoiditis at or near the site of injection of intrathecal penicillin has developed. It is difficult to be certain that this condition is entirely due to the drug, for the penicillin in the cases cited was given for a meningitis, which rarely has a localized arachnoiditis as a sequela.

Cerebral Reactions.—Besides toxic reactions on the spinal cord, large doses

of penicillin administered intrathecally may induce cerebral reactions in the form of convulsions, coma and even death.[27, 28] In man, apparently, a relatively large amount of penicillin may be tolerated, but in the monkey 20,000 units injected in the lumbar subarachnoid space has induced epileptic attacks, coma and death within 12 hours. Neymann, *et al.*,[16] however, has reported two severe reactions with convulsive manifestations, coma and death from the administration of 50,000 Oxford units in the cisterna magna for the treatment of dementia paralytica. Although Neymann, *et al.*, suggests that these manifestations are due to impurities in the penicillin, animal experimentation[28] has shown that pure crystalline penicillin has identical convulsive properties to commercial preparations. Moreover, the convulsive and antibiotic factors appear to be approximately equally affected by various means of inactivation. We believe that it is the penicillin itself which is responsible for the convulsive manifestations.

Convulsive reactions are more likely to occur following intraventricular injection of the drug or its topical application to the cerebral cortex. In dogs and monkeys approximately 500 Oxford units so administered is sufficient to induce epileptic manifestations.[11] Although man can tolerate much larger doses in either site, convulsive reactions have been reported. Probably many more have occurred, but have been considered the result of the primary condition for which the penicillin was being administered. One of the authors knows of several cases in which convulsive seizures developed within five minutes to nine hours after instillation of penicillin into a cerebral abscess or brain sinus. That they were the result of the therapy is difficult to determine because other organic pathologic conditions equally potentially epileptogenic were present. Yet the patients had had no previous seizures, although their pathologic lesion had been present for months.

PENICILLIN THERAPY IN SPECIFIC NERVOUS CONDITIONS

Penicillin therapy has been found of great value in a wide variety of infections of the central nervous system. Some of these may be effectively treated by other chemotherapeutic agents; others respond only to penicillin.

Meningitis.—The meningitides, as a group, have responded very well to penicillin therapy. When a case is suspected of being meningitis, the therapy of choice would appear to be penicillin since it is effective against a greater number of organisms than any other chemotherapeutic agent. If the diagnostic spinal puncture yields a cloudy fluid, the immediate intrathecal injection of 10,000 Oxford units of penicillin seems advisable. This will induce and maintain an antibiotic concentration of pencillin in the cerebrospinal fluid for approximately 24 hours. During that time the infective agent may be determined; its penicillin-resistance estimated, and the advisability of further systemic and/or intrathecal therapy considered. If the patient does not improve clinically within 24–48 hours a change to, or the addition of, sulfonamides may be wise. Intracisternal injection of penicillin will give a much

better dispersion of the drug than the lumbar injection and may be advisable if a temporary improvement begins to regress. Relapses probably indicate a focus which is loculated and not accessible to the mode of administration employed. Intraventricular injection may eliminate such foci. However, at times pneumo-encephalography or ventriculography is needed to locate a loculated leaking subarachnoid or subdural abscess.

Meningococcic Meningitis.—This type of meningitis has responded very well to sulfonamide therapy—the recovery rate being 89–98.7 per cent with this form of treatment. In fact, Keefer[12] states that sulfadiazine is the drug of choice in these infections, although he believes that if improvement

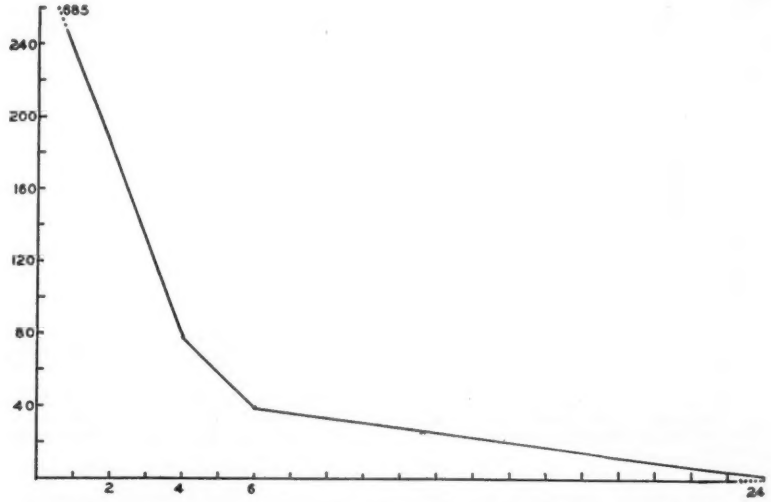


CHART 1.—Showing the concentration of penicillin in the lumbar spinal fluid of man (average of nine cases) after injection of 20,000 Oxford units by lumbar puncture. (The ordinates represent Oxford units of penicillin per cc.; the abscissa hours after injection).

is not apparent within 24–48 hours penicillin should be used. Rarely the two drugs may be required in combination. Since the meningococcus is quite sensitive to penicillin, intramuscular administration of penicillin is frequently adequate to control the disease.[24] Craig, *et al.*,[5] and Meads, *et al.*,[15] question the need for intrathecal penicillin in meningococcic meningitis.

Streptococcic Meningitis.—Although Kolmer[14] states that sulfonamide therapy is superior to penicillin in streptococcic meningitis, in some instances the latter drug has proven more successful. Many strains of streptococci are quite sensitive to the drug. In general, however, intrathecal administration of the drug as well as systemic injection will be required. When the meningitis is secondary to a focus in or about the skull, surgical treatment of that focus is essential to a successful outcome.

Staphylococcic Meningitis.—Since this type of infection is less amenable to sulfonamide therapy, penicillin is particularly desirable in its treatment.

Although only a few cases of staphylococcus meningitis have been reported as treated by this drug[7] the results have been quite satisfactory. Both systemic and intrathecal administration of penicillin appear to be desirable.

Pneumococcic Meningitis.—This type of meningitis formerly was uniformly fatal. Sulfonamide therapy reduced its mortality; penicillin has still lowered it to approximately 50 per cent.[14] Since the pneumococcus is more resistant to penicillin than the streptococcus and staphylococcus, a high con-

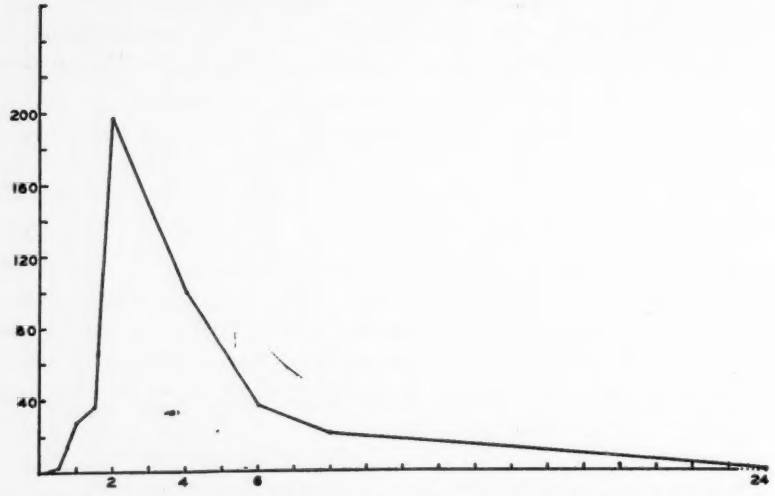


CHART 2.—Showing the concentration of penicillin in the lumbar spinal fluid of man (average of nine cases) after injection of 20,000 Oxford units by cisternal puncture. (The ordinates represent Oxford units of penicillin per cc.; the abscissa hours after injection).

centration is necessary in the spinal fluid. Administration should, therefore, be both systemic and intrathecal. The systemic route is important since many of these cases have a bacteriemia.[17] Probably penicillin combined with sulfadiazine is superior to either drug alone. In some cases intraventricular injections of penicillin may be necessary, particularly if an hydrocephalus develops due to fibrosis about the foramina of Luschka and Magendie at the base of the brain.

Compound Fractures of the Skull with Brain Damage.—The mortality from penetrating war wounds of the skull and brain has been materially decreased by the use of penicillin. Although the evidence that penicillin prophylactically decreases infection is not satisfactory,[6] there is no doubt that in the presence of infection penicillin allows surgical procedures to be carried out which would otherwise be impossible. It is no substitute for débridement and all authors emphasize that dirt, hairs, bone chips, necrotic brain, blood and foreign bodies must be removed if the full effect of the drug is to be realized. Cairns[2] advocates the application of penicillin powder (5,000 Oxford units of penicillin per gram of one of the sulfonamides) to recent brain and scalp wounds with primary closure. In older wounds he advises

irrigation of the wound through a tube twice daily for three to five days. The policy of many surgeons is to débride the wound radically, dust in sulfadiazine, and/or instill 5,000–20,000 units of penicillin, dry or in aqueous solution, and close the wound without drainage, giving systemic penicillin for several days to a week. The great majority of wounds so treated will heal *per primam*. If the cerebral wound has penetrated into the ventricle, intrathecal penicillin may be advisable.

Brain Abscess.—Penicillin and sulfonamide therapy have materially changed the clinical picture of brain abscess. Whereas, formerly the symptoms of acute cerebral infection were present for days or weeks before the abscess became encapsulated, now little clinical evidence of an encephalitis is seen. Any patient with a compound wound of the head who continues to complain of headache and/or whose wound is slow in healing must be suspected of harboring an intracranial abscess. Systemic penicillin in doses of 200,000–300,000 units daily should be given before the abscess is evacuated or extirpated. Intrathecal penicillin may also be advisable if meningeal signs are present. Although injection of penicillin into the abscess cavity after aspiration of pus may sterilize the cavity, usually drainage or extirpation is required before the cavity can be obliterated. At the time of drainage instillation of 1,000–20,000 Oxford units of penicillin in solution or in a vaselined pack may decrease the likelihood of spread of infection. If meningitis has been preëminent, intrathecal administration of penicillin may be necessary. The systemic penicillin should be continued for at least a week after drainage of the abscess.

Spina Bifida.—Infected meningoceles and meningomyeloceles usually respond well to local injection of penicillin (probably 1,000 to 10,000 Oxford units injected every day or two into the sac through normal skin is the optimal dosage). Not only does the infection subside but the thin ulcerated parchment-like skin over the sac heals, becomes thickened and shrinking, decreases the size of the elevated mass. The scar is so firm that surgical repair may not be required.[29]

Other Nervous Conditions.—Penicillin has a favorable effect on early cases of neurosyphilis.[25] The spinal fluid findings improve in 74 per cent of cases. In late neurosyphilis the results are also encouraging. Systemic administration usually of large doses of penicillin has been used in most cases. Intrathecal injection does not seem to have any particular advantages, and in large doses severe reactions have been reported.[16] Penicillin has been tried in a number of other diseases of the nervous system, including tuberculus meningitis, brain tumor,[5] multiple sclerosis, amyotrophic lateral sclerosis and cerebral degeneration, without any evidence that it affects the course of the disease.[11]

SUMMARY

The sensitivity of the infective organisms to penicillin is the guide to the concentration of the drug necessary in the spinal fluid for control of any disease of the central nervous system. By systemic administration alone

concentrations as high as 0.3 Oxford units/cc. may be attained in cases of meningitis, although in normal individuals little, if any, penicillin reaches the cerebrospinal fluid. Higher concentrations may be obtained by intrathecal injection of 10,000 Oxford units. A better distribution of penicillin is gained by cisternal than by lumbar injection, but the latter is a much safer procedure. Large doses of penicillin administered intrathecally are likely to cause meningeal or neural reactions in the form of fever, pleocytosis, radiculitis, convulsions, coma and even death. The therapy for the specific diseases is discussed.

BIBLIOGRAPHY

1 Abraham E. P., Chain, E., Fletcher, C. M., Gardner, A. D., Heatley, N. G., Jennings, M. A., and Florey, H. W.: Further Observations on Penicillin. Lancet, **2**, 177–189, 1941.

2 Cairns, H.: Penicillin in Head and Spinal Wounds. Brit. J. Surg., **32**, 199–207, 1944.

3 Cooke, J. V.: A Simple Clinical Method for the Assay of Penicillin in Body Fluids and for the Testing of Penicillin Sensitivity of Bacteria. J. A. M. A., **127**, 445–449, 1945.

4 Cooke, J. V., and Goldring, D.: The Concentration of Penicillin in Various Body Fluids during Penicillin Therapy. J. A. M. A., **127**, 80–87, 1945.

5 Craig, W. M., Thompson, G. J., Hutter, A. M., Barksdale, E. E., Pfeiffer, C. R., and Woolley, P. V., Jr.: Penicillin: A Progress Report. U. S. Naval M. Bull., **44**, 453–479, 1945.

6 Cutler, E. C., Morton, P. C., and Sandusky, W. R.: Observations on the Prophylactic Use of Penicillin in the Wounds of Aerial Warfare. Brit. J. Surg., **32**, 207–211, 1944.

7 Evans, A. L.: The Treatment of Intracranial Infections with Penicillin: Report of Three Cases. J. A. M. A., **124**, 641–643, 1944.

8 Garrod, L. P., and Heatley, N. G.: Bacteriological Methods in Connection with Penicillin Treatment. Brit. J. Surg., **32**, 117–125, 1944.

9 Harford, C. G., Martin, S. P., Hageman, P. O., and Wood, W. B., Jr.: Treatment of Staphylococcic, Pneumococcic, Gonococcic and other Infections with Penicillin. J. A. M. A., **127**, 253–259, 325–329, 1945.

10 Herrell, W. E.: The Clinical Use of Penicillin. J. A. M. A., **124**, 622–627, 1944.

11 Johnson, H. C., and Walker, A. E.: Unreported observations.

12 Keefer, C. S.: Penicillin: Its Present Status in the Treatment of Infections. Philadelphia Med., **40**, 969–979, 1945.

13 Keefer, C. S., Blake, F. G., Marshall, E. K. Jr., Lockwood, J. S., and Wood, W. B. Jr.: Penicillin in the Treatment of Infections: A Report of 500 Cases (statement by the Committee on Chemotherapeutic and other Agents, Division of Medical Sciences, National Research Council). J. A. M. A., **122**, 1217–1224, 1943.

14 Kolmer, J. A.: Penicillin Therapy including Tyrothricin and other Antibiotic Therapy. New York City, D. Appleton-Century Co. 1945, 318 pp.

15 Meads, M., Harris, W., Stamper, B. A., and Finland, M.: The Treatment of Meningococcal Meningitis with Penicillin. New England J. M., **231**, 509–517, 1944.

16 Neymann, C. A., Heilbrunn, G., and Youmans, G. P.: Experiments in the Treatment of Dementia Paralytica with Penicillin. J. A. M. A., **128**, 433–434, June 9, 1945.

17 Pilcher, C., and Meacham, W. F.: The Chemotherapy of Intracranial Infections. IV—The Treatment of Pneumococcus Meningitis by Intrathecal Administration of Penicillin. J. Neurosurg., **1**, 76–81, 1944.

18 Rammelkamp, C. H., and Keefer, C. S.: Penicillin: Its Antibacterial Effect in Whole Blood and Serum for the Hemolytic Streptococcus and Staphylococcus Aureus. J. Clin. Invest., **22**, 649–657, 1943.

19 Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion and Toxicity of Penicillin Administered by Intrathecal Injection. Am. J. Med. Sc., **205**, 342–350, 1943.

20 Rammelkamp, C. H., and Keefer, C. S.: The Absorption, Excretion, and Distribution of Penicillin. J. Clin. Invest., **22**, 425–437, May, 1943.

21 Robinson, H. J.: Toxicity and Efficacy of Penicillin. J. Pharmac. & Exp. Therap., **77**, 70–79, 1943.

22 Rosenberg, D. H., and Arling, P. A.: Treatment of Cerebrospinal Fever with Penicillin: A Preliminary Report. U. S. Naval Bull., **43**, 281–287, 1944.

23 Rosenberg, D. H., and Arling, P. A.: Penicillin in the Treatment of Meningitis. J. A. M. A., **125**, 1011–1017, 1944.

24 Rosenberg, D. H., and Sylvester, J. C.: The Excretion of Penicillin in the Spinal Fluid in Meningitis. Science, **100**, 132–133, 1944.

25 Stokes, J. H., Sternberg, T. H., Schwartz, W. H., Mahoney, J. F., Moore, J. E., and Wood, W. B. Jr.: The Action of Penicillin in Late Syphilis, Including Neurosyphilis, Benign Late Syphilis and Late Congenital Syphilis: Preliminary Report. J. A. M. A., **126**, 73–80, 1944.

26 Sweet, L. K., Dumoff-Stanley, E., Dowling, H. F., and Lepper, M. H.: The Treatment of Pneumococcic Meningitis with Penicillin. J. A. M. A., **127**, 263–267, 1945.

27 Walker, A. E., Johnson, H. C., and Funderburk, W. H.: Convulsive Factor in Commercial Penicillin. Arch. Surg., **50**, 69–73, 1945.

28 Walker, A. E., Johnson, H. C., and Kollros, J. J.: Penicillin Convulsions: The Convulsive Effects of Penicillin Applied to the Cerebral Cortex of Monkey and Man. Surg., Gynec. & Obst. (in press).

29 Walker, A. E., and Johnson, H. C.: Penicillin Therapy for Spina Bifida. Presented to Chicago Neurol. Soc., May, 1945.

TRAUMATIC RUPTURE OF THE SPLEEN

LT. COL. HARWELL WILSON, M.C., A.U.S.
MEMPHIS, TENN.

TRAUMATIC RUPTURE of the spleen is not an uncommon intra-abdominal accident. Because of the great importance of early diagnosis and proper treatment, because of the diagnostic and therapeutic difficulties in certain atypical cases, and because the increased incidence of this condition is both apparent and real, it seems worth while to briefly review certain important aspects of the problem. Most reports in the literature deal with one or two cases. Such reports convey the impression that the incidence is much lower than is actually the case. Wright and Prigot[1] found that one out of every 666 accident cases admitted to the Harlem Hospital, of New York City, suffered from a ruptured spleen. Roettig, Nusbaum and Curtis[2] found splenic rupture to be present in one out of every 920 accident admissions to the University of Ohio teaching hospital.

The incidence of splenic rupture has become more apparent as diagnosis has improved; however, there is little doubt that the increase is also a real one, due to a larger number of traumatic incidents resulting from motor accidents, industrial injuries, and injuries received by both civilians and soldiers as a result of war. Of special importance is the fact, emphasized by Zabinski and Harkins[3], that in approximately one out of seven cases of splenic rupture the serious hemorrhage is of the secondary type. This now well-established clinical syndrome is especially treacherous and deserves further emphasis in the literature. Splenic rupture is the most common as well as one of the most serious closed intra-abdominal injuries due to trauma. Even in cases where the only intra-abdominal injury is splenic rupture the prognosis is grave, unless diagnosis and treatment are both early and accurate. The frequency with which such lesions are associated with other traumatic injuries make the correct diagnosis and management more difficult and increases the mortality rate. In civilian life, splenic rupture is seen more frequently in closed intra-abdominal injuries. Our impression is that in battle casualties splenic rupture is due in a higher percentage of cases to penetrating intra-abdominal wounds. In cases of obvious penetration of the peritoneal cavity, the surgeon is always obligated to explore the cavity, whereas, in closed injuries, especially in cases with severe associated lesions, it is likely to be more difficult to know the proper course to follow. The type and relative frequency of various associated lesions has been pointed out by Wright and Prigot, and by Roettig, Nusbaum and Curtis, as shown in Tables II and III.

ANATOMY AND PHYSIOLOGY

A few pertinent facts regarding the anatomy and physiology of the spleen are of special benefit in enabling one better to properly manage the cases being considered. The spleen is a very vascular organ composed of friable lymphoid tissue held together by a network of thin fibrous

TABLE I

INCIDENCE OF RUPTURE OF THE SPLEEN IN CASES OF SUBCUTANEOUS ABDOMINAL INJURIES

(*Wright and Prigot*[1])

	No. of Cases	Percentage
Subcutaneous Rupture:		
Spleen	30	47.6
Liver	18	28.6
Intestines	11	17.5
Mesentery	3	4.7
Pancreas	1	1.6
	63	100.0

TABLE II

ASSOCIATED INJURIES IN 22 CASES OF SPLENIC RUPTURE

(*Roettig, Nusbaum and Curtis*)[2]

Type of Injury	Incidence
Fractured ribs	5
Hemothorax	3
Fracture of extremities	3
Contusion of pancreas	1
Ruptured kidney	2
Retroperitoneal hemorrhage	1
Ruptured liver	2

TABLE III

ASSOCIATED INJURIES IN 30 CASES OF SPLENIC RUPTURE

(*Wright and Prigot*)[1]

Associated Lesions	No. of Cases
Fractured ribs	10
Broken bones (simple or compound fractures)	8
Lacerated kidney	6
Hemothorax, pneumothorax, lacerated lung	4
Cerebral complications, fractured skull, lacerated brain	3
Ruptured liver	3
Ruptured Urinary bladder	1
Ruptured diaphragm	1

trabeculae and a thin fibrous capsule. The organ is almost entirely surrounded by peritoneum, being suspended by two of its folds, the phrenicosplenic and gastrosplenic ligaments. The splenic artery is the largest branch of the celiac axis, and, with the exception of the renal vessels, is the largest visceral artery in this region of the body.[4] Michels called attention to the fact that the position of the splenic artery is as variable as is that of the cystic artery[5].

The spleen being suspended in the left upper quadrant, is protected to a certain extent by the cushioning effect of the surrounding structures —the diaphragm superiorly, the stomach and intestines medially and inferiorly, and by the lower chest wall anteriorly. This mechanism of suspension, while protecting the organ to a certain extent, also permits it to be fractured by *contrecoup* as well as by direct violence in certain instances.

The pathologically enlarged spleen, regardless of the cause of the enlargement, has no such protection, and the liability of such spleens to rupture from relatively mild trauma is well known.

The celiac plexus supplies autonomic fibers to the spleen. Stimulation of these fibers causes contraction of the organ to occur. There still remains much to be learned regarding the physiology of the spleen. During the past two decades our knowledge concerning the physiology of the spleen has been greatly augmented due to the studies of Barcroft[6], Doan, Curtis and Wiseman[7], Mann[8], and Holman[9]. Three of its functions which are well-established are as follows: The formation of lymphocytes in the malpighian corpuscles; the destruction of formed elements of the blood; and the storage of blood[10]. This blood reserve may be drawn into the circulation during periods of emergency. It is known that the spleen undergoes contraction during periods of asphyxia, exercise, hemorrhage and emotional excitement. Barcroft and Nisimaru have demonstrated that the spleen is constantly contracting and expanding at intervals of approximately 30 to 60 seconds. These changes in splenic volume are reflected as minor changes in the mean blood pressure. It is generally believed that removal of the spleen has no detrimental effect on the general health or growth of the individual.

DIAGNOSIS

The fact that no single sign is pathognomonic of rupture of the spleen has been pointed out repeatedly. In most cases the diagnosis is made from a history of injury to the left side, followed by signs of peritoneal and diaphragmatic irritation coupled with a clinical picture of hemorrhagic shock.

The most frequent early findings are those of abdominal pain associated with tenderness and rigidity. These findings may be limited to the left upper quadrant of the abdomen, or there may be generalized abdominal findings. Pain in the left shoulder region, due to irritation of the diaphragm, is a fairly common symptom. This is often referred to as Kehr's sign. An area of increased dullness to percussion in the splenic region, Ballance's sign,[12] while not present in all cases, certainly should be looked for. In some instances a definite fluid wave has been demonstrated prior to operation. The signs of hemorrhagic shock found in splenic rupture are no different from those produced by a sudden extensive loss of blood in any other region. There may be pallor, cold clammy skin, mental confusion, a normal or subnormal temperature, tachycardia, and a falling blood pressure. In some instances, due to vasoconstriction, the body is able to com-

pensate for a rather extensive loss of blood before findings of pronounced shock are evident.

Roentgenologic examination is likely to show an area of increased density in the left upper abdominal quadrant, and there may or may not be an elevation of the left diaphragm[13]. Examination of the peripheral blood usually shows a leukocytosis and a gradually developing anemia.

In questionable cases, some authors have advised a diagnostic abdominal paracentesis to demonstrate the presence of blood in the peritoneal cavity. This is not always a reliable procedure, for in some instances this method will lead one away from the correct diagnosis by failing to demonstrate an extensive accumulation of blood walled-off by the omentum and vicera.

Three cases, each serving to emphasize different problems in the management of splenic rupture are reported briefly.

CASE REPORTS

Case 1.—C. S., a combat soldier, was admitted to the hospital complaining of pain in the right lower quadrant of the abdomen. The patient began to experience generalized abdominal pain of moderate severity 24 hours prior to admission. He became nauseated and vomited once. Six hours before admission the pain became localized in the right lower quadrant. There was no history of a previous similar attack.

The past history revealed that one week before admission the patient had been knocked down by the concussion of a shell burst on the Anzio beachhead. The concussion was so severe that the patient was thrown against the ground about ten feet from where he was standing. He fell upon his left side. The patient felt shaken up and slightly bruised but did not feel that he was seriously injured. Following this incident he spent three days in an Evacuation Hospital before returning to his unit. During the three days following the explosion the patient felt faint on three occasions, but never fainted. He experienced no pain in the left shoulder or in the abdomen while at the Evacuation Hospital.

Physical Examination.—Temperature 100° F., pulse 80, and respiration 24. *Chest:* Scattered râles present over left chest posteriorly. *Abdomen:* Tenderness and slight rigidity in right lower quadrant, most marked at McBurney's point. The patient was tender on the right side by rectal examination. *Laboratory Data:* Chest film—Normal. W. B. C. 16,700; R. B. C. 4,000,000; hemoglobin 85 per cent; lymphocytes 28 per cent. Urine normal. *Preoperative Diagnosis:* Acute appendicitis.

Operation.—A right muscle-splitting incision was made. The peritoneum was opened and a large amount of fluid which had the appearance of whole blood welled-up through the incision. Suction was used and the appendix was delivered. The distal half of the appendix was edematous and distended. Appendicectomy was performed, the stump being inverted. There was no evidence of a Meckel's diverticulum, and the abdomen was closed. It was felt that the blood in the abdominal cavity represented both an old and a recent hemorrhage. In view of the patient's injury one week previously, a tentative diagnosis of delayed hemorrhage from traumatic rupture of the spleen was made. The appendicectomy had been performed under a low novocaine spinal anesthetic. Ether and oxygen were given, and a left rectus incision was made. The spleen was examined and found to be torn at the lower pole. Large clots were present and some fresh bleeding was occurring. Splenectomy was performed without difficulty. During the operation, 2000 cc. of sanguineous fluid which had the appearance of whole blood was aspirated from the abdominal cavity. The blood pressure remained at a normal level throughout the procedure; however, 500 cc. of plasma was given during the operation and 500 cc. of whole blood was given after the completion of the operation.

Pathologic Examination: The appendix, in its distal half, is extended and the wall is edematous. There is no fibrin on its surface. The lumen is obstructed by a fecolith.

The spleen was sent to a General Medical Laboratory. The report submitted by Lt. Col. Tracy B. Mallory, M.C., was as follows: Specimen consists of a spleen, measuring 10 x 8 x 5 centimeters. Capsule is grey-brown and slightly wrinkled. Beneath the splenic notch is a splenical enlargement covered by intact capsule, but appearing dark purple in color. There is a small linear tear at the hilus, two centimeters in length. On cut-section the splenic pulp is red-brown in color except for an area, 4 x 1.5 centimeters, lying beneath the discolored portion of the capsule. This area is deep purple in color, and soft in consistence. A small hemorrhagic area one centimeter in diameter is found in the pulp in the upper pole.

Microscopic Examination: Sections show focal areas of parenchymal and subcapsular hemorrhage. There is an early polymorphonuclear response in some regions and a small zone of infarct necrosis, probably due to the presence of ischemia, is seen. *Pathologic Diagnosis:* Ruptured spleen. Multiple hematomata of spleen.

Postoperative Course: The patient developed bronchopneumonia following operation. This responded promptly to sulfadiazine, and his recovery was otherwise uneventful. Three weeks following operation the patient had recovered entirely and the blood studies were normal.

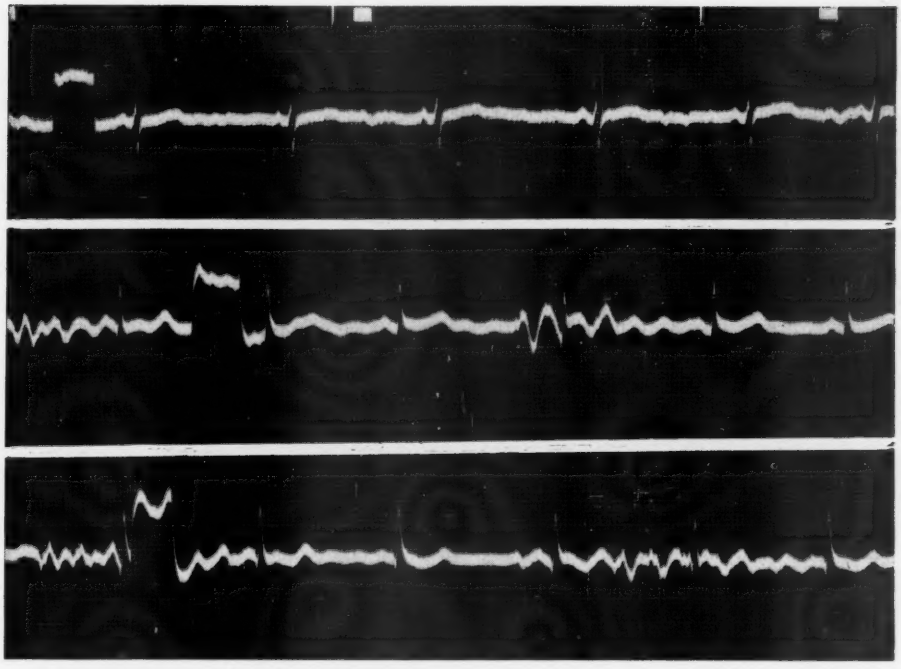
Case 2.—J. C., a well-developed young soldier, while working as a lineman fell from a pole after receiving an electrical shock. The patient struck his head and left shoulder against the ground at the time of the fall. At 4:20 P. M., one-half hour after the fall, this man was brought to the hospital.

Physical Examination: The findings of severe traumatic shock were present, and it was impossible to obtain a blood pressure reading or to palpate the pulse on admission. There was a superficial electrical burn of the right hand and penis. Over the occipital region was a deep irregular laceration, approximately 14 centimeters long. The patient was unable to move his legs, and anesthesia was present below the nipple level. The patient was placed in the shock position and was given 750 cc. of plasma, followed by 500 cc. of blood. He was seen in consultation by Major William Beswick, M.C., neurosurgeon, who felt that it was best at the time to apply simply a sterile dressing to the shaved scalp and to delay, for the time being, any operative repair.

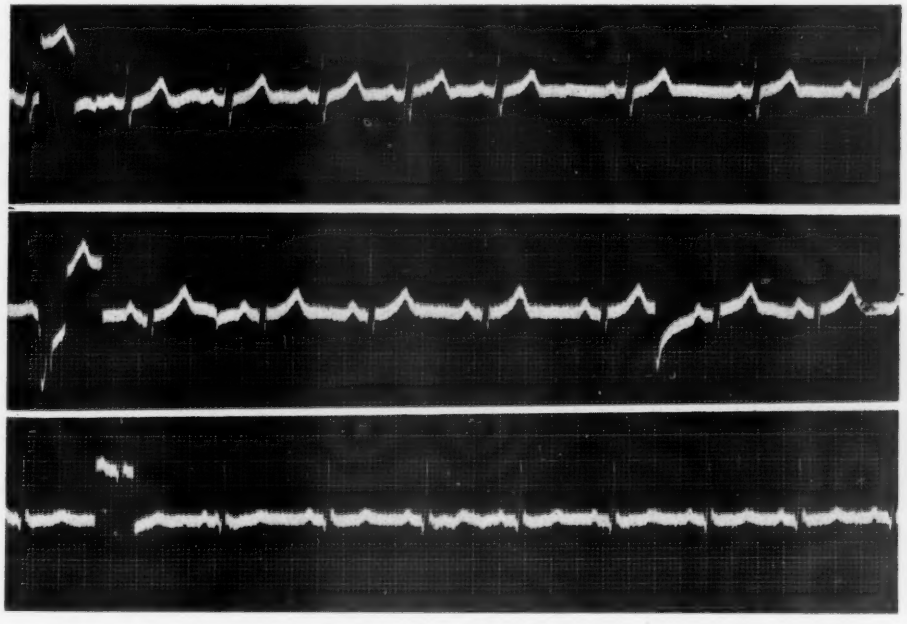
The patient was moved by litter a short distance to the Recovery Ward, and the blood pressure again fell to 60/30. The pressure returned to 110/70 following the administration of 1,000 cc. of whole blood and another 250 cc. unit of plasma. Examination at this time showed the patient to have no complaints except that of some discomfort about the scalp wound and in the region of the left shoulder, upon which he had fallen. The abdomen was soft, and there was no evidence of fracture of any of the long bones.

At 3 A. M. the blood pressure had fallen to 80/40, and the patient again showed all the signs of severe hemorrhagic shock. The abdomen was soft, and no masses could be felt. There was no fluid wave; however, shifting dullness was present in the left flank. A diagnosis of rupture of the spleen with severe intra-abdominal hemorrhage was made. It was realized that the patient also suffered from a lesion of the spinal cord at the level of D-4, and from a severe scalp laceration.

Operation.—Celiotomy was done without any anesthetic agent being necessary because of the cord injury. Oxygen and blood replacement therapy were continued throughout the operation, which was begun with the patient in a state of shock. Blood was not apparent when the abdominal cavity was first opened. After the omentum was withdrawn the left side of the abdomen was found to contain a large amount of clotted and unclotted blood. The spleen was lacerated in two places and a retroperitoneal hematoma was present in the left renal area. Splenectomy was performed and the abdomen was closed with through-and-through heavy silk sutures. At the end of this procedure the blood pressure had returned to 102/70. The scalp was then repaired, local anesthesia being



GRAPH 1.—E. K. G. tracing (on sixth postoperative day) showing evidence of severe myocardial damage characterized by atrioventricular fibrillation flutter and auriculoventricular block.



GRAPH 2.—E. K. G. (one month after first E. K. G.) curve is approaching that of a normal tracing, indicating marked improvement in the cardiac mechanism.

used. During the course of the operation 1,000 cc. of blood and 500 cc. of plasma were administered.

One week after splenectomy a laminectomy was performed by Major William Beswick, M.C. At the site of the compression fracture of the fourth dorsal vertebra the spinal cord was found to be partially severed due to trauma produced by fragments of bone. The patient withstood the operation satisfactorily; however, motor function and sensation were not improved as a result of the cord section. The patient was eventually evacuated to the Zone of Interior.

Case 3.—S., a 14-year-old school boy, was admitted to the hospital one hour after his school bus had been struck by a train. The pulse and blood pressure were not obtainable on admission; however, after the patient had been placed in the shock position and given intravenous fluids the pressure was found to be 105/65. Examination revealed a five-centimeter laceration of the scalp, abrasions of the left chest and abdomen, and superficial abrasions of the extremities. Tenderness was present in the left upper abdominal quadrant. There was slight rigidity of the left rectus muscle in the upper abdomen. A normal urine specimen was obtained.

It was felt that the patient probably had a ruptured spleen, and he was sent to the operating room by way of the Roentgenologic Laboratory. No fractures of bones were found. In the plain film of the abdomen the left upper quadrant was more dense than normal. The psoas shadow on the left side was obliterated. This was interpreted as being suggestive of hemorrhage from a ruptured abdominal viscus. The chest film was normal.

The patient was taken immediately to the operating room. The movement of the patient apparently affected the blood pressure adversely, as the systolic pressure fell to 84 as the operation was begun. A 500-cc. blood transfusion was administered during the operation and another similar transfusion was given after the operation.

Operation.—The abdomen was explored through a left rectus incision. The abdominal cavity seemed to be filled with blood and fresh bleeding was seen to be occurring from the spleen. The pedicle was compressed with the left hand and the incision was enlarged by making a short lateral, or T-shaped, extension. Splenectomy was performed and the abdomen was closed without drainage after the blood had been removed by aspiration. The scalp laceration was sutured.

The postoperative course was relatively uneventful for four days. The patient was slightly distended, but passed flatus and had a normal bowel movement on the fourth postoperative day. The pulse, which was usually regular, varied between 90 and 110 much of the time. The urine at this time was normal.

On the sixth postoperative day a marked irregularity of the pulse was noted (Graph 1). The rate varied, at times being found to fluctuate between 38 and 65. A medical consultant, Dr. Lyle Motley, studied the patient at this time and felt that the arrhythmia was due to cardiac trauma at the time of the accident. It was felt that there might be a fracture of some myocardial fibers. No specific therapy was advised and the consultant felt that the prognosis would probably be favorable.

On the ninth postoperative day, because of abdominal cramps and distention associated with vomiting and constipation, a diagnosis of intestinal obstruction was made.

A right rectus incision revealed an obstruction of the lower ileum at a point where the bowel was adherent to the anterior abdominal wall. When the bowel was separated from the anterior abdominal wall an abscess containing 50 cc. of pus was opened into, and it was seen that a small perforation of the ileum had apparently existed, which had become sealed over. A purse-string suture was used to close the bowel opening. A Witzel ileostomy was done, and two rubber tissue drains were left in the abdomen and brought out *via* stab wounds, one drain leading to the site of the abscess cavity near the abdominal wall, and the other being placed in the pelvis.

There was an unexplained hematuria for a few days following the operation. The urine returned to normal without any specific therapy. The course after this was uneventful except for a small abscess in the abdominal wall, which was drained under local anesthesia. The patient left the hospital approximately eight weeks after admission. At this time, his abdominal wall was well healed, the pulse rate was normal, and studies of the blood, urine and electrocardiogram were normal (Graph 2).

DISCUSSION.—Each of the cases presented serves to emphasize certain important problems in the diagnosis and treatment of splenic rupture. Case 1 came to the hospital with a diagnosis of acute appendicitis, which was verified at operation. The finding of a large collection of blood in the peritoneal cavity, coupled with the history of being thrown against the ground one week previously, made the diagnosis of splenic rupture with delayed hemorrhage seem likely. It is believed that the spleen was injured at the time of the shell concussion one week prior to the development of acute appendicitis. Hemorrhage no doubt occurred at the time of this injury and was probably responsible for the patient feeling quite faint on three occasions, although he never actually fainted. It seems likely that additional blood was being lost from the splenic rupture even though no symptoms were present which could be attributed directly to this. Blood in the right colic gutter can, without question, produce pain which simulates acute appendicitis; however, examination of the appendix showed it to be definitely inflamed. This then, is a case of splenic rupture with delayed hemorrhage which was operated upon during the latent or silent period, the condition being brought to our attention because the patient chanced to develop acute appendicitis at the same time.

The syndrome of delayed hemorrhage from splenic rupture is important, dangerous, and not nearly so uncommon as one might be led to believe from the paucity of material on the subject found in the literature[13, 14, 15]. In most cases there is a history of some type of trauma to the splenic region followed later by the findings of peritoneal irritation and hemorrhagic shock, these findings being due to the presence of the blood lost into the peritoneal cavity. The blood in the abdominal cavity most commonly causes pain, tenderness and rigidity in the left upper quadrant, but these findings may be generalized, and in one reported case the physical signs were present only in the right lower quadrant. The blood from the ruptured spleen may cause diarrhea or constipation due to ileus. Distention may be present. McIndoe[14], in 1932, studied 46 cases representing cases collected from the literature, and his own case. He stimulated much of the subsequent interest in the subject. Recently Zabinski and Harkins[3] have made a comprehensive review of the literature and summarize the findings gained from a study of 179 cases of delayed hemorrhage from splenic rupture.

Case 2 shows the importance of considering the spleen as a source of internal hemorrhage even in the absence of pain, tenderness or rigidity of the abdomen. Shifting dullness in the left flank was demonstrated in this case. The fact that blood was not visible when the abdomen was opened,

until after the omentum was withdrawn, stresses the fallacy of relying upon abdominal paracentesis as a criterion for diagnosis.

Cases 2 and 3 were both operated upon with the patients in a state of shock. The operation was considered imperative and was, in fact, a part of the treatment for shock, as it was necessary to control the active bleeding. In both instances blood was given during and after the operation. These cases also stress the necessity of performing major surgery to preserve life even in the presence of such severe associated injuries as fracture of the dorsal spine with partial section of the spinal cord and severe trauma to the myocardium. The successful treatment of such cases calls for surgical intervention combined with immediate blood replacement therapy.

A few cases are reported where minor splenic fractures were successfully treated by tamponade or suture, but these methods offer far less security from future hemorrhage than does splenectomy. Studies of reported cases reveal a surprising number of wound disruptions occurring as complications in these cases. This has frequently been secondary to pancreatic injury which occurred at the time of the splenectomy. Such injuries can best be avoided by the individual ligation of splenic vessels near the hilum and the avoidance of mass ligatures which may inadvertently include some pancreatic tissue.

SUMMARY AND CONCLUSIONS

1. The incidence of traumatic rupture of the spleen is believed to be increasing due to more accurate diagnosis and to an increase in traumatic accidents encountered by civilians and soldiers.

2. The anatomy and physiology of the spleen are reviewed as related to the management of splenic rupture.

3. Traumatic splenic rupture is the most frequent, as well as one of the most serious, subcutaneous intra-abdominal injuries.

4. The importance of recognition of the syndrome of splenic rupture with delayed hemorrhage is emphasized.

5. Splenectomy combined with adequate blood replacement therapy is the treatment of choice, and this should be instituted as soon as the diagnosis is reasonably established.

BIBLIOGRAPHY

[1] Wright, L. T., and Prigot, A.: Traumatic Subcutaneous Rupture of the Normal Spleen. Arch. Surg., **39**, 551–576, 1939.

[2] Roettig, L. C., Nusbaum, W. D., and Curtis, G. M.: Traumatic Rupture of the Spleen. Amer. Jour. Surg., **59**, No. 2, 292–319, 1943.

[3] Zabinski, E. J., and Harkins, H. N.: Delayed Splenic Rupture: A Clinical Syndrome Following Trauma. Arch. Surg., **46**, 186–213, 1943.

[4] Gray, Henry: Anatomy of the Human Body, 24th Edit., 607, 723, Lea & Febiger, Philadelphia, 1942.

[5] Michels, N. A.: The Variational Anatomy of the Spleen & Splenic Artery. Amer. J. Anat., **70**, 21–72, 1942.

[6] Barcroft, J., *et al.:* Observations upon the Effect of High Altitude on the Physiological Processes of the Human Body. On the Relation of External Temperature to Blood Volume. Phil. Tr. Roy. Soc., B., **211**, 351, 1922. Observations on the Taking up of Carbon Monoxide by the Hemoglobin in the Spleen. J. Physiol., **58**, 138, 1923. Contribution on the Physiology of the Spleen. *Idem Obid.:* **60**, 443, 1925. The Influence of the Spleen in Carbon Monoxide Poisoning. *Idem, Ibid.:* p. 79. Rhythmical Contractions of the Spleen. *Idem, Ibid.:* **74**, 294, 1932. Cause of Rhythmical Contractions of the Spleen. *Idem, Ibid.:* p. 299. Undulatory Changes in Blood Pressure. *Idem, Ibid.:* p. 311. The Action of the Splanchnic Nerves on the Spleen. *Idem, Ibid.:* p. 321. Some Observations on the Denervated Spleen. *Idem, Ibid.:* **87**, 189, 1936.

[7] Doan, C. A., Curtis, G. M., and Wiseman, B. K.: Hemolytopoietic Equilibrium and Emergency Splenectomy. J. A. M. A., **105**, 1567, 1935.

[8] Mann, F. C.: Functions of the Spleen. Indiana Univ. Seminar, March, 1932.

[9] Holman, E.: Significance of Temporary Elevation of Blood Pressure following Splenectomy, with Particular Reference to Rôle of Spleen as Regulator of Circulation. Surg., **1**, 688, 1937.

[10] Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, 2nd Edit. 1939, William & Wilkinson Co., Baltimore, page 83.

[11] Kehr; cited by Bailey: Bailey, H.: Traumatic Rupture of the Normal Spleen. Brit. J. Surg., **15**, 40–46, July, 1927.

[12] Ballance, C. A.: On Splenectomy for Rupture without External Wound: With Remarks on the Symptoms Produced by Removal of the Organs. Practitioner, **60**, 347–358, 1898.

[13] Deaver, J. M.: Delayed Hemorrhage Following Traumatic Rupture of Spleen: With Particular Reference to Roentgenologic Findings. ANNALS OF SURGERY, **113**, 477–480, 1941.

[14] McIndoe, A. H.: Delayed Hemorrhage Following Traumatic Rupture of the Spleen. Brit. J. Surg., **20**, 249–268, 1932.

[15] Harkins, H. N.: Delayed Splenic Rupture. Am. J. Surg., **57**, 159–161, July, 1942.

ACUTE HYPERTENSION WITH SODIUM PENTOTHAL ANESTHESIA IN NEUROLOGIC SURGERY

JACK I. WOOLF, M.D.
CHICAGO, ILL.

FROM THE DIVISION OF NEUROLOGICAL SURGERY, UNIVERSITY OF CHICAGO, CHICAGO, ILL.

THE USE OF SODIUM PENTOTHAL as a surgical anesthetic agent continues to increase in popularity. This is especially true in cases where extensive muscular relaxation is not required. For this reason, many neurosurgeons are using intravenous sodium pentothal anesthesia in all intracranial surgery, usually with the exclusion of suboccipital and cervical exposures. Despite the fact that many of these operations are quite lengthy—frequently lasting three and four hours—no adverse criticism has been brought forth. There are, however, very few reports of any unusual reactions that may occur in its use in neurologic surgery.

One particular phenomenon that has occurred with surprising frequency is an elevation of blood pressure occurring during the subtemporal approach for a retrogasserian neurectomy when performed under sodium pentothal anesthesia. Woodall and Goodman[21] have noted this reaction but felt that it was due to stimulation of the gasserian ganglion. Lundy[11] mentions that he has noted vascular hypertension once or twice in intracranial surgery when pentothal anesthesia was used. The type of case or procedure, however, is not described. The vascular effect most frequently mentioned has been a mild hypotension correlated with the rapidity and amount of pentothal used.[13, 17] This was thought to be due to a reduced sympathetic activity.[12] Other signs of a state of sympathetic hypoactivity is a reduced peripheral resistance[16] and raised skin temperature.[2] Allen, Lundy and Adson[2] used intravenous pentothal as a preoperative indication for sympathectomies. They believe that it gave an accurate reflection of the fall in blood pressure that ensued after upper lumbar and splanchnic resections.

Gruber, *et al.*,[8] and Burstein and Ravenstine,[5] have shown from work on animals that the parasympathetic (cardiac vagus) system is hypersensitive during sodium pentothal anesthesia. Further evidence of autonomic hypersensitivity, noted by Bishop and Rudder[4] has been the repeated appearance of bradycardia during ocular enucleations only when performed under intravenous pentothal anesthesia. They felt that this was "a manifestation of the oculocardiac reflex plus the parasympathetic action of pentothal sodium."

In animal experimentation, Reynolds[15] failed to note a fall in blood pressure when sodium pentothal was injected slowly and just sufficiently to stop respirations. A second dose given after the return of reflexes caused an increased pulse pressure, but without "significant alteration of the systolic pressure." Draper and Whitehead,[6] likewise, found the blood pressure maintained at normal levels in dogs during surgical anesthesia, with a fall during

the toxic stage. After respiratory arrest had been maintained and anoxemia had developed, the blood pressure level rose.

Elevations in blood pressure have been reported with sodium pentothal anesthesia in rabbits[19] and dogs.[7, 9] An initial fall in pressure in half of the dogs was followed by a secondary rise which surpassed the control pressure in 90 per cent of the experiments. The maximum rise was 77 mm. of mercury. In some a pure rise in pressure occurred.

MATERIAL AND METHODS

The present report comprises observations on blood pressure changes which occurred during the subtemporal surgical approach to the retrogasserian ganglion in a group of 20 cases. In order that a control might be established, a second group of 20 cases of extirpation of herniated intervertebral disks were studied also. A series of ten consecutive cases from each group operated upon under intravenous sodium pentothal anesthesia was compared to a similar series operated upon under other anesthesia.

The method of surgical exposure of the gasserian ganglion was similar in all cases. In each instance the patient was placed in a sitting position and a vertical incision was made in the temporal region. The temporal fascia and muscle were incised, the bone was trephined and enlarged to the size of a silver dollar. After the dura mater was stripped from the floor of the middle fossa, the foramen spinosum was plugged with cotton and the middle meningeal artery cut. The dura propria was elevated from the covering of the ganglion which was incised and the retrogasserian fibers avulsed. At the completion of the avulsion, jugular compression was performed to verify hemostasis.

A routine technic in extirpation of the herniated intervertebral disks was carried out. The patient was placed in a prone jack-knife position with the trunk horizontal. The paravertebral muscles were separated subperiosteally from the spines and lamina. After excising the ligamentum flavum, the dura and nerve root were retracted medially, the annulus fibrosus incised and the greater portion of the disk removed.

Premedication consisted of .0004 to .0006 Gm. atropine sulfate in all cases, and either morphine sulfate .01 Gm. or calcium nembutal .18 to .27 Gm. These were usually administered one hour before surgery. No significant change could be correlated with the latter two drugs.

Intravenous anesthesia was always started with a 2.5 per cent solution of pentothal by syringe. After narcosis was well induced, a 1 per cent solution—usually by the slow continuous drip method—was used to maintain the desired level throughout the remainder of the procedure. Surgery usually was begun immediately after anesthesia was induced. Inhalation of either 100 per cent oxygen or oxygen plus nitrous oxide—50 per cent each—was given. In four cases in which oxygen plus nitrous oxide was used the average rise in pressure was almost identical with the cases in which only oxygen had been used. The average amount of pentothal used in the subtemporal approach

was 1.65 Gm., and in the spinal cases it was 2 Gm. The increased amount used in the latter group was due to a lengthier operative time. Supplementary fluids or stimulants were not required in any case.

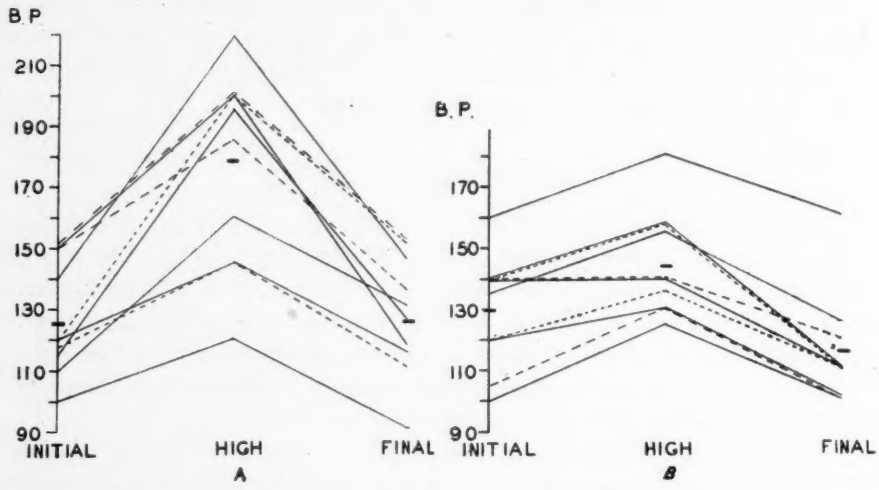


CHART 1.—Showing blood pressure readings before surgery (initial), the highest level occurring during surgery (high), and at the completion of the operation (final) for retrogasserian neurectomy by the subtemporal approach are shown.

The elevation in blood pressure under sodium pentothal anesthesia (A), may be compared with that under ether anesthesia (B).

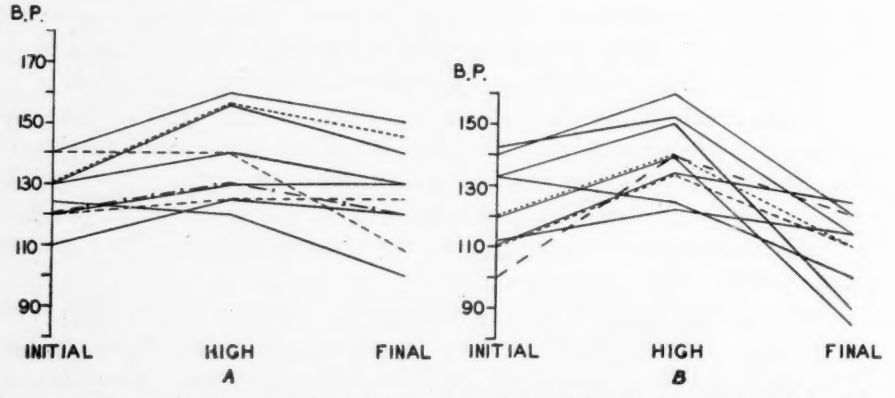


CHART 2.—Showing blood pressure levels during extirpation of herniated intervertebral disks under sodium pentothal (A) and ether (B) anesthesias are illustrated.

RESULTS

Under sodium pentothal anesthesia there was a marked rise in blood pressure when performing the retrogasserian operation. The average rise in systolic pressure was 51.3 mm. of mercury and in diastolic pressure 32.5 mm. The elevated blood pressure was usually maintained throughout the period of intracranial manipulation and was not limited to the time during which the retrogasserian fibers were being exposed and avulsed. There was seldom an associated rise in pulse rate of any consequence. During the latter part of

the intracranial procedure the pressure began to fall and was essentially normal at the end of the operation. In several cases it was noted that the return to the preoperative level took a precipitous drop immediately after bilateral jugular compression. The changes in each case are shown in Chart 1. The initial blood pressure, that which was taken by the anesthetist prior to anesthesia, averaged 125.5/76 mm. of mercury. The average highest reading was 176.8/108.5 mm., and the average final reading was 124.5/79.0 mm. of mercury. Two points are of particular interest in these figures. First, the rise in pressure is far above that which is likely to occur either from irritation of a peripheral nerve or as a coincidental reaction. Second, the final pressure at the end of the operation was essentially the same as the preoperative level.

In the subtemporal series operated upon under ether anesthesia the average systolic elevation was 14.1 mm. of mercury. The average diastolic elevation was negligible—only 0.17 mm. As might be expected from general surgical experiences, the final blood pressure was approximately 15 mm. of mercury lower.

The results of blood pressure variations in the spinal operations are depicted in Chart 2. It is at once obvious that there are no essential differences during the operative procedures. There was a slight rise in both series done under pentothal and under ether anesthesia. The average rise in the former was 11/8.7 mm. of mercury and in the latter 17/9 mm. of mercury. A point of interest, however, is the final level. This is similar to that occurring in intracranial surgery with sodium pentothal in that the final pressure was identical with the preoperative level despite an operative time varying from 1.5 to 3 hours and an average requirement of 2 Gm. pentothal.

To obviate the effect of pentothal anesthesia upon postural vascular tension, a series of 15 patients with convulsive seizures were studied before performing a pneumo-encephalogram. Intravenous sodium pentothal was given with the patient supine. Blood pressures were taken at one to three minute intervals. No constant changes were noted during or after the induction phase; however, a slight fall in pressure was frequently noted. The patient was tilted to an upright sitting posture. Blood pressures were taken at 30°, 60°, and 90° and similarly on being lowered. There were no constant or striking changes associated with the position. Occasionally a 10 to 15 mm. fall in pressure was noted after the anesthesia was induced; a somewhat similar fall or rise ensued after the patient was placed in the sitting position.

Discussion.—The acute hypertensive phenomenon noted in subtemporal craniectomy procedures under pentothal anesthesia is presented both for its physiologic and clinical interest. The hypertension in some of the cases was quite striking, reaching a maximum elevation of 85 mm. of mercury. There are several important clinical factors. Gruber, Haury and Gruber[9] felt from their experimental work on dogs that the general systemic blood pressure elevation might be a definite contraindication for the use of this drug in cases of hypertension or cardiac damage. This would seem logical since in dogs cardiac arrythemia was routinely produced under this anesthesia. "In those experi-

ments in which cardiac arrythemia was not instituted by the injection of pentothal sodium, the arrythemia could usually be introduced by increasing the blood pressure upon withdrawal of the carotid sinus reflex." In the present series, however, only one case of cardiac arrythemia was noted under sodium pentothal anesthesia. In this case an elevation in blood pressure of 30 mm. Hg. was followed by a cardiac fibrillation. This occurred after two hours of anesthesia. The fibrillation lasted about five minutes but was insufficient to produce gross signs of circulatory embarrassment. The cardiac rhythm returned to normal with a sudden drop in blood pressure. Since this was at the end of the surgical procedure, at which time the usual drop occurred, it was not possible to determine whether the fall in pressure mitigated the fibrillation or whether the fibrillation caused the fall in pressure.

Despite the fact that many of the patients in this group had mild generalized arteriosclerosis, with slight cardiac enlargement, their general postoperative recovery appeared smoother than the cases performed under ether anesthesia.

An important point noted has been in the normalcy of the blood pressures in both groups operated upon under pentothal anesthesia. This was present despite occasional lengthy operating time and use of rather large doses of sodium pentothal, and would tend to refute any detectable deleterious effect of pentothal upon the circulatory or cardiac system.

Several authors have suggested that pentothal should not be used in cases of shock. However, the findings in the present cases, particularly the normal blood pressures at the end of the operative procedures would tend to suggest a converse opinion. This factor has been substantiated (Pender and Essex[14]) by showing a delayed development of shock and death in dogs under pentothal as compared to ether anesthesia. Adams and Gray[1] verify this clinically.

The cause of the hypertension in the present cases is not clear. The possibility of irritation to the trigeminal nerve does not appear likely since the elevation in blood pressure was usually encountered before the nerve was reached and persisted to a slight extent after all the fibers were avulsed. If pain alone were a factor, a similar elevation would be expected upon retraction of the sensory roots during disk operations and also on cutting the trigeminal root by the suboccipital approach. This did not occur. It is more probable that an hypersensitivity of the cerebral vasomotor centers takes place under pentothal anesthesia. Parasympathetic overactivity has been shown in experimentation on cats.[5] In the discussion of the hypertension found in dogs[9] no postulation as to the underlying mechanism was made. The possibility of increased intracranial pressure *per se*, due to retraction and pressure upon the unopened dura, has been considered but has been discarded for several reasons: (1) A lowered intracranial pressure has been shown to be present under sodium pentothal anesthesia.[10, 21] (2) Intracranial pressure is lessened at the time of incising the sheath of gasserian ganglion with the escape of cerebrospinal fluid. (3) Hypertension was not present in those cases operated upon under ether anesthesia.

SUMMARY

A definite acute arterial hypertension has been noted during the subtemporal approach to the gasserian ganglion when performed under sodium pentothal anesthesia. The average elevation in blood pressure in a series of ten consecutive cases was 51.3/32.5 mm. of mercury. Under ether anesthesia such an elevation does not occur—the average in a similar series being 141.1 mm. of mercury. In a comparative series of pentothal and ether anesthesias for the extirpation of herniated intervertebral disks, no specific elevation of blood pressure was seen. The average pressure being 11/8.7 and 17/9 mm. of mercury, respectively.

The final blood pressure in both series, however, was higher when pentothal was used, thus, suggesting that operative or postoperative shock is less likely to occur under pentothal anesthesia.

The possibility of a postural hypertensive effect under pentothal sodium was eliminated. It appears more likely that an increased sensitivity of the central vasomotor centers occurs during pentothal anesthesia. Since the retraction of the temporal lobe probably results in a rather widespread pressure or irritative effect, the site of the vasomotor stimulation is not known.

BIBLIOGRAPHY

[1] Adams, R. C., and Gray, H. K.: Intravenous Anesthesia with Pentothal Sodium in the Case of Gunshot Wound Associated with Accompanying Severe Traumatic Shock and Loss of Blood: Report of a Case. Anesthesiology, **4**, 70–73, 1943.

[2] Allen, E. V., Lundy, J. S., and Adson, A. W.: Preoperative Prediction of Effects on Blood Pressure of Neurosurgical Treatment of Hypertension. Proc. Staff Meet., Mayo Clin., **11**, 401-406, 1936.

[3] Beecher, H. K.: The Physiology of Anesthesia. Oxford University Press, New York, 1938.

[4] Bishop, H. F., and Rudder, F. F.: Intravenous Anesthesia. J. A. M. A., **120**, 807-810, 1942.

[5] Burstein, C. L., and Rovenstine, E. A.: Respiratory Parasympathetic Action of some Shorter-acting Barbituric Acid Derivatives. J. Pharmacol. & Exper. Therap., **63**, 42–50, 1938.

[6] Draper, W. B., and Whitehead, R. W.: Diffusion Respiration in the Dog Anesthetized by Pentothal Sodium. Anesthesiology, **5**, 262-273, 1944.

[7] Gruber, C. M.: The Effects of Anesthetic Doses of Sodium Thio-pentobarbital, Sodium Thio-ethymol and Pentothal Sodium upon the Respiratory System, the Heart and Blood Pressure in Experimental Animals. J. Pharmacol. and Exper. Therap., **60**, 143-173, 1937.

[8] Gruber, C. M., Gruber, C. M., Jr., and Colosi, N. A.: The Irritability of the Cardiac Vagus Nerves as Influenced by the Intravenous Injections of Barbiturates, Thiobarbiturates and Picrotoxin. J. Pharmacol. & Exper. Therap., **63**, 215-228, 1938.

[9] Gruber, C. M., Haury, V. G., and Gruber, C. M., Jr.: The Cardiac Arrhythmia, Characteristic Effect of the Thio-barbiturates as Influenced by Changes in Arterial Blood Pressure. J. Pharmacol. & Exper. Therap., **63**, 193-213, 1938.

[10] Horsely, J. S.: The Intracranial Pressure during Barbital Narcosis. Lancet, **1**, 141-143, 1937.

[11] Lundy, J. S.: Clinical Anesthesia. W. B. Saunders, Philadelphia, 1942.

[12] Marshall, S. V.: "Pentothal Sodium" Anesthesia: A Review with an Analysis of 333 Cases. Med. J. Aust., **26**, 382-391, 1939.

[13] **Palmer, E. P.:** Basic Intravenous Anesthesia with Sodium Ethyl Thio-barbiturate. South. Med. J., **32,** 290-294, 1939.

[14] **Pender, W. P., and Essex, H. E.:** A Study of Traumatic Shock under Certain Anesthetics. Anesthesiology, **4,** 247-252, 1943.

[15] **Reynolds, C.:** Dangers of Prolonged Pentothal Sodium Anesthesia from the Pharmacological Standpoint. Anesth. and Analg., **18,** 270-273, 1939.

[16] **Smith, C. H.:** Use of Sodium Pentothal Anesthesia for a Patient with a Tendency to Thrombosis and Embolism. Proc. Staff Meet. Mayo Clin., **12,** 239-240, 1937.

[17] **Thomas, G. J.:** Pentothal Sodium: Pharmacologic Action, Range of Usefulness, Complications and their Management. Anesth. and Analg., **23,** 8-15, 1944.

[18] **Walker, E.:** Discussion of Paper by D. H. Stubbs. South Med. J., **34,** 1051-1057, 1941.

[19] **Werner, J.:** The Effect of Evipal and Pentothal on Blood Pressure. J. Pharmacol. & Exper. Therap., **60,** 122-123, 1937.

[20] **White, J. C., Verlot, M., Selverstone, B., and Beecher, H. K.:** Changes in Brain Volume During Anesthesia: The Effects of Anoxia and Hypercapnia. Arch. Surg., **44,** 1-21, 1942.

[21] **Woodhall, B., and Goodman, E.:** Pentothal Sodium Anesthesia in Neurologic Surgery, War Med., **4,** 556°564, 1943.

Note: The cases used in this report were obtained largely from the neurologic service of Dr. A. E. Walker.

INDEX TO VOLUME 122

A

ABBOTT, WILLIAM E., *et al.*: Metabolic Alterations Following Thermal Burns, 122, 678.

Abdomen and Thorax, Combined Injuries of the, 122, 358.

Abdominal Pain, Left-sided; (Epiploic Appendicitis, a Cause of, 122, 126; Symptoms, Serum Amylase Findings in Chronic Alcoholic Patients with Acute, 122, 117.

Acoustic Trauma, 122, 1086.

Acute Hypertension with Sodium Pentothal Anesthesia in Neurologic Surgery, 122, 1146.

ADAMS, W. E., *et al.*: The Use of Blood Plasma for Filling the Pleural Space Following Total Pneumonectomy, 122, 905.

ADAMS, WILLIAM E.; and CLARK, DWIGHT EDWIN: Transthoracic Esophagogastrostomy for Benign Strictures of the Lower Esophagus, 122, 942.

Adrenalectomy, Bilateral, in Prostatic Cancer, 122, 1031.

Advanced Carcinoma of the Extrahepatic Bile Ducts: Choleangiocholecystocholedochectomy, 122, 522.

Ainhum (Dactylolysis Spontanea), 122, 868.

AKIN, JOHN T., JR.; and ELMAN, ROBERT: A Design for Surgical Convalescence, 122, 716.

Alcoholic Patients with Acute Severe Abdominal Symptoms, Serum Amylase Findings in Chronic, 122, 117.

Amylase, Serum, Findings in Chronic Alcoholic Patients with Acute Severe Abdominal Symptoms, 122, 117.

Anesthesia, Coma During and Following, Spinal, 122, 278; for Men Wounded in Battle, 122, 807; the Present Status of Ethylene-oxygen, 122, 1071; Sodium Pentothal, Acute Hypertension with, in Neurologic Surgery, 122, 1146.

Aneurysm, Arteriovenous, 122, 529; Traumatic, of the First Portion of the Left Vertebral Artery, 122, 102.

Antitoxin, Value of, in the Prevention and Treatment of Malignant Edema and Gas Gangrene, 122, 197.

Antrum Gastritis, Chronic Hypertrophic, 122, 235.

Appendicitis, Acute, the Local Use of Sulfanilamide in the Treatment of, 122, 625; Acute, and Malaria, The Simultaneous Occurrence of, 122, 432; Epiploic; a Cause of Left-Sided Abdominal Pain, 122, 126.

ARENDT, JULIAN: Chronic Hypertrophic Antrum Gastritis, 122, 235.

Arm and Hand, Direct Flap Repair of Defects of the, 122, 706.

Arterial Injuries in a Theater of Operations, 122, 223.

Arteriovenous Aneurysm, 122, 529; Fistula, the Immediate and Late Treatment of an, 122, 210.

Artery, the Left Vertebral, Traumatic Aneurysm of the First Portion of, 122, 102.

B

BAILEY, PERCIVAL: Chronic Leptomeningeal Thickening Following Treatment of Meningitis with Sulfa-drugs, 122, 917.

Battle, Anesthesia for Men Wounded in, 122, 807; Casualties, a Study of Shock in, 122, 745.

BECKER, WALTER F., *et al.*: Muco-epidermoid Tumors of Salivary Glands, 122, 820.

BEECHER, HENRY K.: Anesthesia for Men Wounded in Battle, 122, 807.

BELINKOFF, STANTON: Coma During and Following Spinal Anesthesia, 122, 278.

Benign Capillary Hemangioma of Digital Flexor Tendon Sheath, 122, 444.

BETTS, REEVE H.: Thoraco-abdominal Injuries, 122, 793.

BIGELOW, ROBERT R., and BRUNSCHWIG, ALEXANDER: Advanced Carcinoma of the Extrahepatic Bile Ducts: Choleangiocholecystocholedochectomy, 122, 522.

BIGGER, I. A., and EVANS, EVERETT IDRIS: The Rationale of Whole Blood Therapy in Severe Burns, 122, 693.

Bilateral Adrenalectomy in Prostatic Cancer, 122, 1031.

Bile Duct, Common, the Use of Vitallium Tubes in Strictures and Absence of the, 122, 490.

Bile Ducts, Extrahepatic, Advanced Carcinoma of the: Choleangiocholecystocholedochectomy. 122, 522.

Biliary Fistula, Cholecystogastroduodenocutaneous, 122, 48.

BLAKEMORE, ARTHUR H., and LORD, JERE W., JR.: The Technic of Using Vitallium Tubes in Establishing Portacaval Shunts for Portal Hypertension, 122, 476.

Blood Iodine Studies, 122, 963.

Blood Plasma, Use of, for Filling the Pleural Space Following Total Pneumonectomy, 122, 905.

Blood Therapy, Whole, Rationale of, in Severe Burns, 122, 693.

Blood Vessels, Secondary Hemorrhage Arising from Gunshot Wounds of the Peripheral, 122, 631.

BLOOMFIELD, SYLVAN, and NEUHOF, HAROLD: The Surgical Significance of an Anomalous Cholecystohepatic Duct, 122, 260.

Bone, Experiences with Injuries and Diseases of, in World War II, 122, 23.

Bones, Long, The Pathogenesis of Localized Fibrous Lesions in the Metaphyses of, 122, 1016.

BOOK REVIEW: Essentials of oral Surgery, Reviewed by Douglas B. Parker, 122, 128.

BOOKS RECEIVED, 122, 287.

BROWN, JAMES BARRETT, *et al.*: Direct Flap Repair of Defects of the Arm and Hand, 122, 706.

BRUNSCHWIG, ALEXANDER: Radical Resections of Advanced Intra-abdominal Cancer, 122, 923.

Brunschwig, Alexander, and Bigelow, Robert R.: Advanced Carcinoma of the Extrahepatic Bile Ducts: Choleangiocholecystocholedochectomy, 122, 522.

Bucy, Paul C.: Surgical Relief of Tremor at Rest, 122, 933.

Burford, Thomas H., Parker, Edward F., and Samson, Paul C.: Early Pulmonary Decortication in the Treatment of Posttraumatic Empyema, 122, 163.

Burns, Resurfacing of Dorsum of the Hand, Following, 122, 39; Severe, the Rationale of Whole Blood Therapy in, 122, 693; Thermal, Metabolic Alterations Following, 122, 678.

Byberg, Robert A., and Lam, Corad R.: Epiploic Appendicitis: A Cause of Left-sided Abdominal Pain, 122, 126.

C

Caldwell, Guy A.: Secondary Infection of Wounds, 122, 641.

Campbell, Eldridge H., Jr.: Compound, Comminuted Skull Fractures Produced by Missiles, 122, 375.

Cancer of the Face, 122, 88; Prostatic, Bilateral Adrenalectomy in, 122, 1031.

Cannon, Bradford, *et al.*: Direct Flap Repair of Defects of the Arm and Hand, 122, 706.

Capillary Hemangioma of Digital Flexor Tendon Sheath, Benign, 122, 444.

Carcinoma of the Extrahepatic Bile Ducts, Advanced: Coleangiocholecystocholedochectomy, 122, 522.

Carcinomas, Resection of the Left Lobe of the Liver in a Patient with Four Separate, 122, 1092.

Carlton, L. M., Jr., *et al.*: The Use of Blood Plasma for Filling the Pleural Space Following Total Pneumonectomy, 122, 905.

Carter, Sylvester J.: Serum Amylase Findings in Chronic Alcoholic Patients with Acute Severe Abdominal Symptoms, 122, 117.

Casualties, Battle, a Study of Shock in, 122, 745.

Cataracts, Congenital, Following Rubella in Pregnancy, 122, 1049.

Cattell, Lee M., *et al.*: The Use of Penicillin in the Treatment of Acute Hematogenous Osteomyelitis in Children, 122, 954.

Cecum, Solitary Diverticulitis of the, 122, 52.

Chandy, Jacob: The Use of Heterogenous Fascial Grafts in the Radical Operation for Herniae, 122, 885.

Chest, Injuries of the, and War Wounds, Evacuation Hospital Experiences with, 122, 147.

Choleangiocholecystocholedochectomy: Advanced Carcinoma of the Extrahepatic Bile Ducts, 122, 522.

Cholectystogastroduodenocutaneous Biliary Fistula, 122, 48.

Cholecystohepatic Duct, The Surgical Significance of an Anomalous, 122, 260.

Chronic Hypertrophic Antrum Gastritis, 122, 235; Leptomeningeal Thickening Following Treatment of Meningitis with Sulfa-drugs, 122, 917.

Clark, Dwight Edwin; and Adams, William E.: Transthoracic Esophagogastrostomy for Benign Strictures of the Lower Esophagus, 122, 942.

Cole, Warren H., *et al.*: The Use of Vitallium Tubes in Strictures and Absence of the Common Bile Duct, 122, 490.

Coller, F. A., *et al.*: Translocation of Fluid Produced by the Intravenous Administration of Isotonic Salt Solutions in Man Postoperatively, 122, 663.

Collom, Spencer A., Jr., and Ewing, William McDaniel: A Comparative Study of 100 Fractures of the Shaft of the Femur in which one-half were Treated with Penicillin, 122, 773.

Colon and Rectal Injuries in the Forward Areas, The Surgical Management of, 122, 398.

Coma During and Following Spinal Anesthesia, 122, 278.

Combined Injuries of the Thorax and Abdomen, 122, 358.

Comparative Study of 100 Fractures of the Shaft of the Femur in which One-half were Treated with Penicillin, 122, 773.

Compere, Edward L., *et al.*: The Use of Penicillin in the Treatment of Acute Hematogenous Osteomyelitis in Children, 122, 954.

Complications of Intra-osseous Therapy, 122, 266.

Compound, Comminuted Skull Fractures Produced by Missiles, 122, 375.

Congenital Cataracts Following Rubella in Pregnancy, 122, 1049; Diaphragmatic Hernia, 122, 569; or Hereditary Polyposis of the Colon, 122, 606.

Continuous Traction Screw for Fixation of Fractures of the Hip, 122, 59.

Convalescence, a Design for Surgical, 122, 716.

Copleman, Benjamin, and Keene, Clifford H.: Traumatic Right Diaphragmatic Hernia, 122, 191.

Croce, Edmund J., *et al.*: The Management of War Injuries of the Extraperitoneal Rectum, 122, 408.

Curtis, George M., and Fertman, M. Been: Blood Iodine Studies, 122, 963.

Cutis Grafts, 122, 996.

Cutler, Condict W., Jr.: Profits to Peace-time Practice from Surgical Experiences of War, 122, 734.

D

Davis, William Bowdoin, *et al.*: Direct Flap Repair of Defects of the Arm and Hand, 122, 706.

DeCholnoky, Tibor: Cancer of the Race, 122, 88,

Decortication in the Treatment of Posttraumatic Empyema, Early Pulmonary, 122, 163.

Design for Surgical Convalescence, 122, 716.

Diaphragmatic Hernia, Congenital, 122, 569; Traumatic Right, 122, 191; the Surgical Treatment of the More Common Types of: Esophageal Hiatus, Traumatic, Pleuroperitoneal Hiatus, Congenital Absence and Foramen of Morgagni, 122, 546.

Dilatation of the Esophagus, Idiopathic, 122, 582.

Direct Flap Repair of Defects of the Arm and Hand, 122, 706.

Diverticulitis of the Cecum, Solitary, 122, 52.

Donovan, Edward J.: Congenital Diaphragmatic Hernia, 122, 569.

Dragstedt, Lester R.: Vagotomy for Gastroduodenal Ulcer, 122, 973.

Duct, Cholecystohepatic, The Surgical Significance of an Anomalous, 122, 260; Common Bile, the Use of Vitallium Tubes in Strictures and Absence of the, 122, 490.
Ducts, Extrahepatic Bile, Advanced Carcinoma of the: Choleangiocholecystocholedochectomy, 122, 522.
DUNCAN, ROBERT D., and SKINNER, HOMER L.: Recurrent Inguinal Hernia, 122, 68.

E

Early Pulmonary Decortication in the Treatment of Posttraumatic Empyema, 122, 163.
EBERT, R. V., and EMERSON, C. P.: A Study of Shock in Battle Casualties, 122, 745.
Edema, Malignant, and Gas Gangrene, the Value of Antitoxin in the Prevention and Treatment of, 122, 197.
ELKIN, DANIEL C., and KELLY, ROBERT P.: Arteriovenous Aneurysm, 122, 529.
ELMAN, ROBERT, and AKIN, JOHN T., Jr.: A Design for Surgical Convalescence, 122, 716.
EMERSON, C. P., Jr., and EBERT, R. V.: A Study of Shock in Battle Casualties, 122, 745.
Empyema, Posttraumatic, Early Pulmonary Decortication in the Treatment of, 122, 163.
Enteritis, Regional, 122, 845.
Epiploic Appendicitis; A Cause of Left-sided Abdominal Pain, 122, 126.
Esophagogastrostomy, Transthoracic, for Benign Strictures of the Lower Esophagus, 122, 942.
Esophagus, Idiopathic Dilatation of the, 122, 582; Lower, Transthoracic Esophagogastrostomy for Benign Strictures of the, 122, 942.
Etiology and Treatment of Polycythemia Rubra Vera, 122, 1098.
Evacuation Hospital Experiences with War Wounds and Injuries of the Chest, 122, 147.
EVANS, EVERETT IDRIS, and BIGGER, I. A.: The Rationale of Whole Blood Therapy in Severe Burns, 122, 693.
EWING, WILLIAM MCDANIEL, and COLLOM, SPENCER A., Jr.: A Comparative Study of 100 Fractures of the Shaft of the Femur in which One-half were Treated with Penicillin, 122, 773.
Experiences with Injuries and Diseases of Bone in World War II, 122, 23; with 156 Penetrating Wounds of the Head, 122, 12; with Sympathectomy in Peripheral Lesions, 122, 29; with the Miller-Abbott Tube, a Statistical Study of 1000 Cases, 122, 253.
Extrahepatic Bile Ducts, Advanced Carcinoma of the: Choleangiocholecystocholedochectomy, 122, 522.
Extraperitoneal Rectum, Management of War Injuries of the, 122, 408.

F

Face, Cancer of the, 122, 88; Subtotal Replacement of the Skin of the, 122, 1042.
FARMER, A. W., and WOOLHOUSE, F. M.: Resurfacing of Dorsum of the Hand Following Burns, 122, 39.
Fascial Grafts, Use of Heterogenous in the Radical Operation for Herniae, 122, 885.
Femur, 100 Fractures of the Shaft of the, in which One-half were Treated with Penicillin, A Comparative Study of, 122, 773.
FERTMAN, M. BEEN, and CURTIS, GEORGE M.: Blood Iodine Studies, 122, 963.
FINE, JACOB, *et al.*: Traumatic Shock Incurable by Volume Replacement Therapy, 122, 652.
Fistula, Arteriovenous, the Immediate and Late Treatment of an, 122, 210, Biliary, Cholecystogastroduodenocutaneous, 122, 48.
Flap Repair of Defects of the Arm and Hand, Direct, 122, 706.
FOOTE, FRANK W., *et al.*: Muco-epidermoid Tumors of Salivary Glands, 122, 820.
Fractures, Compound Battle, in the Mediterranean Theater of Operations, Reparative Surgery of, 122, 289; of the Hip, A Continuous Traction Screw for Fixation of, 122, 59; (100) of the Shaft of the Femur in which One-half were Treated with Penicillin, A Comparative Study of, 122, 773; Skull, Produced by Missiles; Compound, Comminuted, 122, 375.
FRANK, HOWARD A., *et al.*: Traumatic Shock Incurable by Volume Replacement Therapy, 122, 652.
FREEMAN, NORMAN E.: Secondary Hemorrhage Arising from Gunshot Wounds of the Peripheral Blood Vessels, 122, 631.

G

Gangrene, Gas, and Malignant Edema, The Value of Antitoxin in the Prevention and Treatment of, 122, 197.
Gas Gangrene, Malignant Edema and, the Value of Antitoxin in the Prevention and Treatment of, 122, 197.
Gastritis, Chronic Hypertrophic Antrum, 122, 235.
Gastroduodenal Ulcer, Vagotomy for, 122, 973.
GATEWOOD, JOHN W.: Solitary Diverticulitis of the Cecum, 122, 52.
GAYNOR, WILLIAM C., and GURWITZ, JACK: Experiences with 156 Penetrating Wounds of the Head, 122, 12.
GESCHICKTER, CHARLES F., and WEBSTER, GEORGE V.: Benign Capillary Hemangioma of Digital Flexor Tendon Sheath, 122, 444.
Glands, Salivary, Muco-epidermoid Tumors of, 122, 820.
Grafts, Cutis, 122, 996; Skin, the Use of, 122, 1.
GRAHAM, WALTER C., *et al.*: Direct Flap Repair of Defects of the Arm and Hand, 122, 706.
GRAY, HOWARD K., and SHARPE, WENDELL S.: Cholecystogastroduodenocutaneous Biliary Fistula, 122, 48.
GRIFFIN, GRACE E., *et al.*: Metabolic Alterations Following Thermal Burns, 122, 678.
GRIMSON, KEITH S.: Blood Pressure of Renal and of Early and Late Neurogenic Hypertension Dogs after Low Cervical Cord Section, 122, 990.
Gunshot Wounds of the Peripheral Blood Vessels, Secondary Hemorrhage Arising from, 122, 631.
GURWITZ, JACK, and GAYNOR, WILLIAM C.: Experiences with 156 Penetrating Wounds of the Head, 122, 12.

H

HALL, IVAN C.: The Value of Antitoxin in the Prevention and Treatment of Malignant Edema and Gas Gangrene, 122, 197.
HAMPTON, OSCAR P.: Reparative Surgery of Compound Battle Fractures in the Mediterranean Theater of Operations, 122, 289.

Hand, Resurfacing of Dorsum of the, Following Burns, 122, 39; and Arm, Direct Flap Repair of Defects of the, 122, 706.
HARKINS, HENRY N.: Cutis Grafts, 122, 996.
HARRINGTON, STUART W.: The Surgical Treatment of the more Common Types of Diaphragmatic Hernia: Esophageal Hiatus, Traumatic, Pleuroperitoneal Hiatus, Congenital Absence and Foramen of Morgagni, 122, 546.
HATCHER, C. HOWARD: The Pathogenesis of Localized Fibrous Lesions in the Metaphyses of Long Bones, 122, 1016.
Head, Wounds of the, Experiences with 156 Penetrating, 122, 12.
Headaches from Lesions of Scalp Nerves, 122, 1056.
HEIFETZ, CARL J.: Traumatic Aneurysm of the First Portion of the Left Vertebral Artery, 122, 102.
Hemangioma, Benign Capillary, of Digital Flexor Tendon Sheath, 122, 444.
Hemorrhage, Secondary, Arising from Gunshot Wounds of the Peripheral Blood Vessels, 122, 631.
Hepatosplenopathies, The Problem of Portal Hypertension in Relation to the, 122, 449.
Hernia, Diaphragmatic, Congenital, 122, 569; Diaphragmatic, the Surgical Treatment of the more Common Types of: Esophageal Hiatus, Traumatic, Pleuroperitoneal Hiatus, Congenital Absence and Foramen of Morgagni, 122, 546; Observations on the Surgical Treatment of, 122, 878; Present Status of the Injection Treatment of, 122, 85; Recurrent Inguinal, 122, 68; Right Paraduodenal, 122, 436; Traumatic Right Diaphragmatic, 122, 191.
Herniae, the Use of Heterogenous Fascial Grafts in the Radical Operation for, 122, 885.
HERTZLER, ARTHUR E.: The Second Five-year Period Experience in Total Thyroidectomy, 122, 862.
Hip, a Continuous Traction Screw for Fixation of Fractures of the, 122, 59.
HIRSHFELD, JOHN W., *et al.*: Metabolic Alterations Following Thermal Burns, 122, 678.
HOLMAN, EMILE: The Immediate and Late Treatment of an Arteriovenous Fistula, 122, 210.
HOWSER, JOHN W., *et al.*: Ainhum (Dactylolysis Spontanea) 122, 868.
HUGGINS, CHARLES, and SCOTT, WILLIAM WALLACE: Bilateral Adrenalectomy in Prostatic Cancer, 122, 1031.
HURT, LAWRENCE E.: The Surgical Management of Colon and Rectal Injuries in the Forward Areas, 122, 398.
Hypertension, Acute, with Sodium Pentothal Anesthesia in Neurologic Surgery, 122, 1146; Portal, the Technic of Using Vitallium Tubes in Establishing Portacaval Shunts for, 122, 476; Problem of Portal, in Relation to the Hepatosplenopathies, 122, 449.
Hypertrophic Antrum Gastritis, Chronic, 122, 235.

I

Idiopathic Dilatation of the Esophagus, 122, 582.
Immediate and Late Treatment of an Arteriovenous Fistula, 122, 210.
Infection, Secondary, of Wounds, 122, 641.
Inguinal Hernia, Recurrent, 122, 68.
Injection Treatment of Hernia, Present Status of the, 122, 85.
Injuries, Colon and Rectal, in the Forward Areas, The Surgical Management of, 122, 398; Combined, of the Thorax and Abdomen, 122, 358; and Diseases of Bone in World War II, Experiences with, 122, 23; Thoraco-abdominal, 122, 793; War, of the Extraperitoneal Rectum, Management of, 122, 408.
Intra-osseous Therapy, Complications of, 122, 266.
Intrathoracic and Thoraco-abdominal Wounds in the Combat Zone, the Management of, 122, 333.
Introduction of Rubber Gloves for Use in Surgical Operations, 122, 902.
IOB, VIVIAN, *et al.*: Translocation of Fluid Produced by the Intravenous Administration of Isotonic Salt Solutions in Man Postoperatively, 122, 663.
Iodine Studies, Blood, 122, 963.
IRENEUS, CARL, Jr., *et al.*: The Use of Vitallium Tubes in Strictures and Absence of the Common Bile Duct, 122, 490.
Isotonic Salt Solutions in Man Postoperatively, Translocation of Fluid Produced by the Intravenous Administration of, 122, 663.

J

JENKINS, HILGER PERRY: Subtotal Replacement of the Skin of the Face, 122, 1042.
JOHNSON, HERBERT C., and WALKER, A. EARL: Principles and Practice of Penicillin Therapy in Diseases of the Nervous System, 122, 1125.
JOHNSON, VANSEL S., *et al.*: The Management of War Injuries of the Extraperitoneal Rectum, 122, 408.

K

KALDER, N. B., *et al.*: Translocation of Fluid Produced by the Intravenous Administration of Isotonic Salt Solutions in Man Postoperatively, 122, 663.
KEENE, CLIFFORD H., and COPLEMAN, BENJAMIN: Traumatic Right Diaphragmatic Hernia, 122, 191.
KELLY, ROBERT P., and ELKIN, DANIEL C.: Arteriovenous Aneurysm, 122, 529.
KELLY, ROBERT P., *et al.*: Traumatic Osteomyelitis: The Use of Skin Grafts, Part I., 122, 1.
KIRTLEY, JAMES A., Jr.: Arterial Injuries in a Theater of Operations, 122, 223; Experiences with Sympathectomy in Peripheral Lesions, 122, 29.
KRAUSE, ARLINGTON C.: Congenital Cataracts Following Rubella in Pregnancy, 122, 1049.
KREDEL, FREDERICK E.: Headaches from Lesions of Scalp Nerves, 122, 1056.

L

LAHEY, FRANK H., and TREVOR, WILLIAM: Right Paraduodenal Hernia, 122, 436.
LAM, CONRAD R., and BYBERG, ROBERT A.: Epiploic Appendicitis: A Cause of Left-sided Abdominal Pain, 122, 126.
Leptomeningeal Thickening, Chronic, Following Treatment of Meningitis with Sulfa-drugs, 122, 917.

Lesions, Localized Fibrous, the Pathogenesis of, in the Metaphyses of Long Bones, 122, 1016; of Scalp Nerves, Headaches from, 122, 1056; Peripheral, Experiences with Sympathectomy, 122, 29.

LINDSAY, J. R.: Osteomyelitis of the Petrous Pyramid of the Temporal Bone, 122, 1060.

LISCHER, CARL E., *et al.*: Direct Flap Repair of Defects of the Arm and Hand, 122, 706.

Liver, Resection of the Left Lobe of the, in a Patient with Four Separate Carcinomas, 122, 1092.

LIVINGSTONE, H. M.: The Present Status of Ethylene-oxygen Anesthesia, 122, 1071.

Local Use of Sulfanilamide in the Treatment of Acute Appendicitis, 122, 625.

LORD, JERE W., Jr., and BLAKEMORE, ARTHUR H.: The Technic of Using Vitallium Tubes in Establishing Portacaval Shunts for Portal Hypertension, 122, 476.

Lymphopathia Venerea, Stricture of the Female Urethra with, 122, 111.

LYONS, JOHN H., and RAINES, SAMUEL L.: Renal Decapsulation for Transfusion Oliguria, 122, 894.

M

MACAUSLAND, W. RUSSELL, and VIRGIN, HERBERT, Jr.: A Continuous Traction Screw for Fixation of Fractures of the Hip, 122, 59.

MACGREGOR, W. W.: Observations on the Surgical Treatment of Hernia, 122, 878.

MAIER, ROLAND L.: The Present Status of the Injection Treatment of Hernia, 122, 85.

Malaria and Acute Appendicitis, The Simultaneous Occurrence of, 122, 432.

Malignant Edema and Gas Gangrene, the Value of Antitoxin in the Prevention and Treatment of 122, 197.

Management of Intrathoracic and Thoraco-abdominal Wounds in the Combat Zone, 122, 333; of War Injuries of the Extraperitoneal Rectum, 122, 408.

Meningitis, Treatment of with Sulfa-drugs, Chronic Leptomeningeal Thickening Following, 122, 917.

Metabolic Alterations Following Thermal Burns, 122, 678.

Metaphyses of Long Bones, the Pathogenesis of Localized Fibrous Lesions in the, 122, 1016.

Miller-Abbott Tube, Experiences with the, a Statistical Study of 1,000 Cases, 122, 253.

MITCHELL, JAMES F.: The Introduction of Rubber Gloves for Use in Surgical Operations, 122, 902.

MOORE, ANDREW M., *et al.*: Direct Flap Repair of Defects of the Arm and Hand, 122, 706.

MOYER, C. A., *et al.*: Translocation of Fluid Produced by the Intravenous Administration of Isotonic Salt Solutions in Man Postoperatively, 122, 663.

Muco-epidermoid Tumors of Salivary Glands, 122, 820.

MUELLER, R. STERLING: The Local Use of Sulfanilamide in the Treatment of Acute Appendicitis, 122, 625.

MURRAY, ROBERT A., *et al.*: Traumatic Osteomyelitis: The Use of Skin Grafts, Part I., 122, 1.

Myoblastoma, 122, 122.

N

NELLER, J. LOCKE: The Use of Fluorescent Wheals in Determining Extent and Degree of Peripheral Vascular Insufficiency, 122, 898.

Nerves, Scalp, Headaches from Lesions of, 122, 1056.

Nervous System, Principles and Practice of Penicillin Therapy in Diseases of the, 122, 1125.

NEUHOF, HAROLD, and BLOOMFIELD, SYLVAN: The Surgical Significance of an Anomalous Cholecystohepatic Duct, 122, 260.

Neurologic Surgery, Acute Hypertension with Sodium Pentothal Anesthesia in, 122, 1146.

NORTH, JOHN P.; and RAVDIN, I. S.: The Simultaneous Occurrence of Acute Appendicitis and Malaria, 122, 432.

O

Observations on the Severely Wounded in Forward Field Hospitals: With Special Reference to Wound Shock, 122, 129.

Observations on the Surgical Treatment of Hernia, 122, 878.

Oliguria, Transfusion, Renal Decapsulation for, 122, 894.

O'NEILL, JAMES F., and TOCANTINS, LEANDRO M.: Complications of Intra-osseous Therapy, 122, 266.

ORR, THOMAS G.: Myoblastoma, 122, 122.

Osteomyelitis, Hematogenous, in Children, the Use of Penicillin in the Treatment of Acute, 122, 954; of the Petrous Pyramid of the Temporal Bone, 122, 1060; Traumatic, 122, 1.

P

Pain, Left-sided Abdominal; Epiploic Appendicitis, a Cause of, 122, 126.

Paraduodenal Hernia, Right, 122, 436.

PARKER, DOUGLAS B.: Essentials of Oral Surgery, Reviewed by, 122, 128.

PARKER, EDWARD F., SAMSON, PAUL C., and BURFORD, THOMAS H.: Early Pulmonary Decortication in the Treatment of Posttraumatic Empyema, 122, 163.

Pathogenesis of Localized Fibrous Lesions in the Metaphyses of Long Bones, 122, 1016.

PATTERSON, F. M. SIMMONS, and PFEIFFER, DAMON B.: Congenital or Hereditary Polyposis of the Colon, 122, 606.

Penicillin, a Comparatice Study of 100 Fractures of the Shaft of the Femur in which One-half were Treated with, 122, 773; Therapy in Diseases of the Nervous System, Principles and Practice of, 122, 1125; the Use of, in the Treatment of Acute Hematogenous Osteomyelitis in Children, 122, 954.

Peripheral Blood Vessels, Secondary Hemorrhage Arising from Gunshot Wounds of the, 122, 631; Lesions, Experiences with Sympathectomy in, 122, 29.

PERLMAN, H. B.: Acoustic Trauma, 122, 1086.

Petrous Pyramid of the Temporal Bone, Osteomyelitis of the, 122, 1060.

PFEIFFER, DAMON B., and PATTERSON, F. M. SIMMONS: Congenital or Hereditary Polyposis of the Colon, 122, 606.

PILLING, MATTHEW A., *et al.*: Metabolic Alterations Following Thermal Burns, 122, 678.

Plasma, Blood, the Use of, for Filling the Pleural Space Following Total Pneumonectomy, 122, 905.
Pleural Space, the Use of Blood Plasma for Filling the, Following Total Pneumonectomy, 122, 905.
Pneumonectomy, the Use of Blood Plasma for Filling the Pleural Space Following Total, 122, 905.
Polycythemia Rubra Vera, The Etiology and Treatment of, 122, 1098.
Polyposis of the Colon, Congenital or Hereditary, 122, 606.
Portacaval Shunts for Portal Hypertension, the Technic of Using Vitallium Tubes in Establishing, 122, 476.
Portal Hypertension, the Technic of Using Vitallium Tubes in Establishing Portacaval Shunts for, 122, 476.
Present Status of Ethylene-oxygen Anesthesia, 122, 1071; of the Injection Treatment of Hernia, 122, 85.
Principles and Practice of Penicillin Therapy in Diseases of the Nervous System, 122, 1125.
Problem of Portal Hypertension in Relation to the Hepatosplenopathies, 122, 449.
Profits to Peace-time Practice from Surgical Experiences of War, 122, 734.
Prostatic Cancer, Bilateral Adrenalectomy in, 122, 1031.
PUGH, H. L.: Regional Enteritis, 122, 845.
Pulmonary, Early, Decortication in the Treatment of Posttraumatic Empyema, 122, 163.

R

RAINES, SAMUEL L., and LYONS, JOHN H.: Renal Decapsulation for Transfusion Oliguria, 122, 894.
Rationale of Whole Blood Therapy in Severe Burns, 122, 693.
RAVDIN, I. S., and NORTH, JOHN P.: The Simultaneous Occurrence of Acute Appendicitis and Malaria, 122, 432.
Rectal and Colon Injuries in the Forward Areas, The Surgical Management of, 122, 398.
Rectum, Extraperitoneal, Management of War Injuries of the, 122, 408.
Recurrent Inguinal Hernia, 122, 68.
Regional Enteritis, 122, 845.
Renal Decapsulation for Transfusion Oliguria, 122, 894.
Reparative Surgery of Compound Battle Fractures in the Mediterranean Theater of Operations, 122, 289.
Resection of the Left Lobe of the Liver in a Patient with Four Separate Carcinomas, 122, 1092.
Resurfacing of Dorsum of the Hand Following Burns, 122, 39.
REYNOLDS, JOHN T., *et al.*: The Use of Vitallium Tubes in Strictures and Absence of the Common Bile Duct, 122, 490.
Right Paraduodenal Hernia, 122, 436.
ROSATI, LOUIS M., *et al.*: Traumatic Osteomyelitis: The Use of Skin Grafts, Part I., 122, 1.
Rubber Gloves, the Introduction of, for Use in Surgical Operations, 122, 902.
Rubella in Pregnancy, Congenital Cataracts Following, 122, 1049.
Rupture of the Spleen, Traumatic, 122, 1136.

S

SAMSON, PAUL C., BURFORD, THOMAS H., and PARKER, EDWARD F.: Early Pulmonary Decortication in the Treatment of Posttraumatic Empyema, 122, 163.
SANGER, PAUL W.: Evacuation Hospital Experiences with War Wounds and Injuries of the Chest, 122, 147.
Scalp Nerves, Headaches from Lesions of, 122, 1056.
SCARBOROUGH, C. PARKE, *et al.*: Direct Flap Repair of Defects of the Arm and Hand, 122, 706.
SCHAFER, PAUL W.: The Etiology and Treatment of Polycythemia Rubra Vera, 122, 1098.
SCHNUTE, WILLIAM J., *et al.*: The Use of Penicillin in the Treatment of Acute Hematogenous Osteomyelitis in Children, 122, 954.
SCOTT, W. J. MERLE: Idiopathic Dilation of the Esophagus, 122, 582.
SCOTT, WILLIAM WALLACE; and HUGGINS, CHARLES: Bilateral Adrenalectomy in Prostatic Cancer, 122, 1031.
Second Five-year Period Experience in Total Thyroidectomy, 122, 862.
Secondary Hemorrhage Arising from Gunshot Wounds of the Peripheral Blood Vessels, 122, 631; Infection of Wounds, 122, 641.
SELIGMAN, ARNOLD M., *et al.*: Traumatic Shock Incurable by Volume Replacement Therapy, 122, 652.
Serum Amylase Findings in Chronic Alcoholic Patients with Acute Severe Abdominal Symptoms, 122, 117.
SHARPE, WENDELL S., and GRAY, HOWARD K.: Cholecystogastroduodenocutaneous Biliary Fistula, 122, 48.
Shock, Traumatic, Incurable by Volume Replacement Therapy, 122, 652; Wound, With Special Reference to: Observations on the Severely Wounded in Forward Field Hospitals, 122, 129.
SHROPSHEAR, GEORGE; *et al.*: Ainhum (Dactylolysis Spontanea), 122, 868.
Simultaneous Occurrence of Acute Appendicitis and Malaria, 122, 432.
Skin Grafts, The Use of, 122, 1.
SKINNER, HOMER L., and DUNCAN, ROBERT D.: Recurrent Inguinal Hernia, 122, 68.
Skull Fractures Produced by Missiles; Compound, Comminuted, 122, 375.
SMITH, BEVERLY C.: Experiences with the Miller-Abbott Tube: A Statistical Study of 1,000 Cases, 122, 253.
SNYDER, HOWARD E.: The Management of Intrathoracic and Thoraco-abdominal Wounds in the Combat Zone, 122, 333.
Solitary Diverticulitis of the Cecum, 122, 52.
Spinal Anesthesia, Coma During and Following, 122, 278.
Spleen, Traumatic Rupture of the, 122, 1136.
STEIN, HYMEN D., and WEEDEN, WILLIS M.: Experiences with Injuries and Diseases of Bone in World War II, 122, 23.

STEWART, FRED W., *et al.*: Muco-epidermoid Tumors of Salivary Glands, 122, 820.
STEWART, JOHN D., and WARNER, FRANK: Observations on the Severely Wounded in Forward Field Hospitals: With Special Reference to Wound Shock, 122, 129.
Stricture of the Female Urethra with Lymphopathia Venerea, 122, 111.
Strictures and Absence of the Common Bile Duct, the Use of Vitallium Tubes in, 122, 490.
Study of Shock in Battle Casualties, 122, 745.
Subtotal Replacement of the Skin of the Face, 122, 1042.
Sulfa-drugs, Chronic Leptomeningeal Thickening Following Treatment of Meningitis with, 122, 917.
Sulfanilamide, the Local Use of, in the Treatment of Acute Appendicitis, 122, 625.
Surgical Management of Colon and Rectal Injuries in the Forward Areas, 122, 398.
Surgical Relief of Tremor at Rest, 122, 933.
Surgical Significance of an Anomalous Cholecystohepatic Duct, 122, 260.
Surgical Treatment of the More Common Types of Diaphragmatic Hernia: Esophageal Hiatus, Traumatic, Pleuroperitoneal Hiatus, Congenital Absence and Foramen of Morgagni, 122, 546.
Sympathectomy in Peripheral Lesions, Experiences with, 122, 29.

T

TAUBER, ROBERT: Stricture of the Female Urethra with Lymphopathia Venerea, 122, 111.
Technic of Using Vitallium Tubes in Establishing Portacaval Shunts for Portal Hypertension, 122, 476.
Temporal Bone, Osteomyelitis of the Petrous Pyramid of the, 122, 1060.
Tendon Sheath, Benign Capillary Hemangioma of Digital Flexor, 122, 444.
Thoraco-abdominal Injuries, 122, 793; Wounds in the Combat Zone, The Management of Intrathoracic and, 122, 333.
Thorax and Abdomen, Combined Injuries of the, 122, 358.
THORNTON, T. F., Jr., *et al.*: The Use of Blood Plasma for Filling the Pleural Space Following Total Pneumonectomy, 122, 905.
Thyroidectomy, the Second Five-year Period, Experience in Total, 122, 862.
TOCANTINS, LEANDRO M., and O'NEILL, JAMES F.: Complications of Intra-osseous Therapy, 122, 266.
Traction Screw, a Continuous, for Fixation of Fractures of the Hip, 122, 59.
Translocation of Fluid Produced by the Intravenous Administration of Isotonic Salt Solutions in Man Postoperatively, 122, 663.
Transthoracic Esophagogastrostomy for Benign Strictures of the Lower Esophagus, 122, 942.
Trauma, Acoustic, 122, 1086.
Traumatic Aneurysm of the First Portion of the Left Vertebral Artery, 122, 102; Osteomyelitis: The Use of Skin Grafts, 122, 1; Right Diaphragmatic Hernia, 122, 191; Shock Incurable by Volume Replacement Therapy, 122, 652; Rupture of the Spleen, 122, 1136.
Tremor at Rest, Surgical Relief of, 122, 933.
TREVOR, WILLIAM, and LAHEY, FRANK H.: Right Paraduodenal Hernia, 122, 436.
Tube, Miller-Abbott, Experiences with the: A Statistical Study of 1,000 Cases, 122, 253.
TUHY, JOHN E., and WELCH, CHARLES STUART: Combined Injuries of the Thorax and Abdomen, 122, 358.
Tumors, Muco-epidermoid, of Salivary Glans, 122, 820.

U

Ulcer, Gastroduodenal, Vagotomy for, 122, 973.
Urethra, Female, Stricture of the, with Lymphopathia Venerea, 122, 111.
Use of Blood Plasma for Filling the Pleural Space Following Total Pneumonectomy, 122, 905; Fluorescent Wheals in Determining Extent and Degree of Peripheral Vascular Insufficiency, 122, 898; Heterogenous Fascial Grafts in the Radical Operation for Herniae, 122, 885; Penicillin in the Treatment of Acute Hematogenous Osteomyelitis in Children, 122, 954; Vitallium Tubes in Strictures and Absence of the Common Bile Duct, 122, 490.

V

Vagotomy for Gastroduodenal Ulcer, 122, 973.
Value of Antitoxin in the Prevention and Treatment of Malignant Edema and Gas Gangrene, 122, 197.
VAN PROHASKA, JOHN: Resection of the Left Lobe of the Liver in a Patient with Four Separate Carcinomas, 122, 1092.
Vascular Insufficiency, Peripheral, the Use of Fluorescent Wheals in Determining Extent and Degree of Peripheral, 122, 898.
VAUGHN, ARKELL M., *et al.*: Ainhum (Dactylolysis Spontanea), 122, 868.
VAUGHN, H. H., *et al.*: Translocation of Fluid Produced by the Intravenous Administration of Isotonic Salt Solutions in Man Postoperatively, 122, 663.
Venerea, Lymphopathia, Stricture of the Female Urethra with, 122, 111.
Vertebral Artery, Traumatic Aneurysm of the First Portion of the Left, 122, 102.
VIRGIN, HERBERT, Jr., and MACAUSLAND, W. RUSSELL: A Continuous Traction Screw for Fixation of Fractures of the Hip, 122, 59.
Vitallium Tubes, Technic of Using, in Establishing Portacaval Shunts for Portal Hypertension, 122, 476; the Use of, in Strictures and Absence of the Common Bile Duct, 122, 490.

W

WALKER, A. EARL, and JOHNSON, HERBERT C.: Principles and Practice of Penicillin Therapy in Diseases of the Nervous System, 122, 1125.
War Injuries of the Extraperitoneal Rectum, Management of, 122, 408.
WARNER, FRANK, and STEWART, JOHN D.: Observations on the Severely Wounded in Forward Field Hospitals: With Special Reference to Wound Shock, 122, 129.

War, Surgical Experiences of; Profits to Peacetime Practice from, 122, 734; Wounds and Injuries of the Chest, Evacuation Hospital Experiences with, 122, 147.

WEBSTER, GEORGE V., and GESCHICKTER, CHARLES F.: Benign Capillary Hemangioma of Digital Flexor Tendon Sheath, 122, 444.

WEEDEN, WILLIS M., and STEIN, HYMEN D.: Experiences with Injuries and Diseases of Bone in World War II, 122, 23.

WELCH, CHARLES STUART, and TUHY, JOHN E.: Combined Injuries of the Thorax and Abdomen, 122, 358.

WHIPPLE, ALLEN O.: The Problem of Portal Hypertension in Relation to the Hepatosplenopathies, 122, 449.

WILSON, HARWELL: Traumatic Rupture of the Spleen, 122, 1136.

WIPER, THOMAS B.; *et al.*: The Management of War Injuries of the Extraperitoneal Rectum, 122, 408.

WOOLF, JACK I.: Acute Hypertension with Sodium Pentothal Anesthesia in Neurologic Surgery, 122, 1146.

WOOLHOUSE, F. M., and FARMER, A. W.: Resurfacing of Dorsum of the Hand Following Burns, 122, 39.

Wound Shock, With Special Reference to: Observations on the Severely Wounded in Forward Field Hospitals, 122, 129.

Wounds, Gunshot, of the Peripheral Blood Vessels, Secondary Hemorrhage Arising from, 122, 631; of the Head, Experiences with 156 Penetrating, 122, 12 Intrathoracic and Thoraco-abdominal, in the Combat Zones, the Management of, 122, 333; Secondary Infection of, 122, 641.

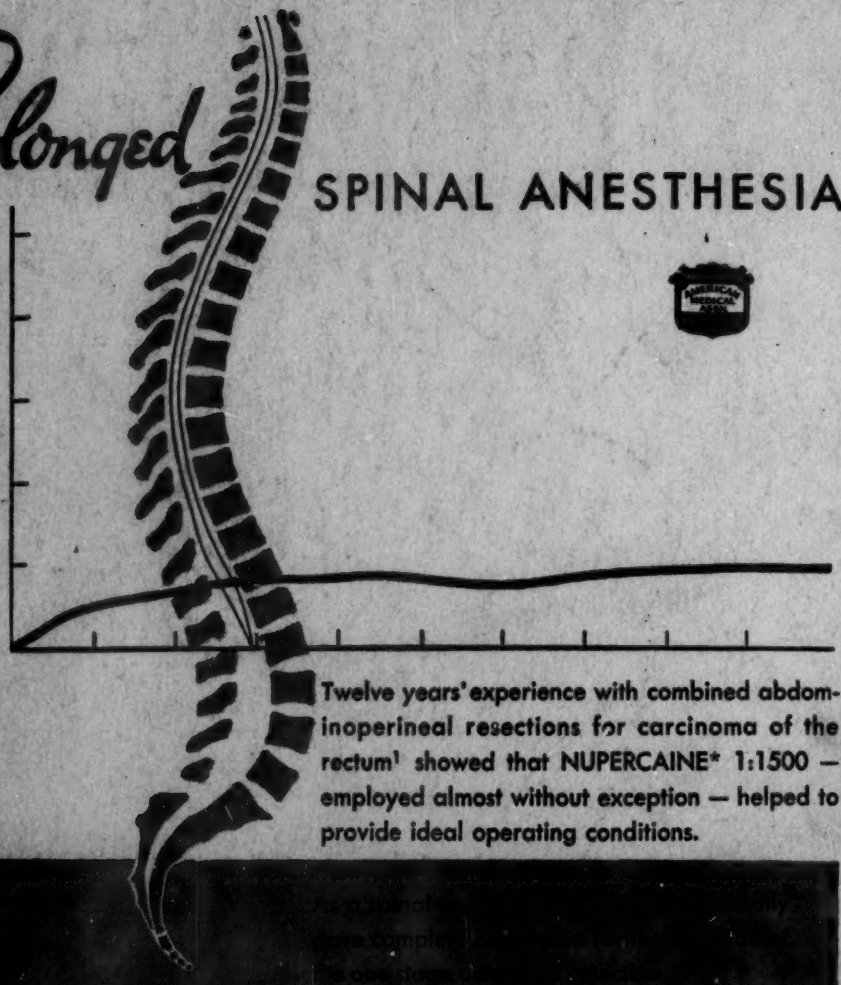
Red comfort

Serenium soothes inflamed genito-urinary membranes while possessing low toxicity and a wide margin of safety. Effective in either acid or alkaline urine, this red dye (diamino-4'-ethoxy-azobenzene hydrochloride) halts the growth of most bacterial urinary invaders. Administered orally, Serenium tablets ease the patient's discomfort and constitute an effective weapon against genito-urinary infections.

SQUIBB *Serenium* TRADEMARK

MANUFACTURING CHEMISTS TO THE MEDICAL PROFESSION SINCE 1858

Prolonged SPINAL ANESTHESIA



Twelve years' experience with combined abdominoperineal resections for carcinoma of the rectum[1] showed that NUPERCAINE* 1:1500 — employed almost without exception — helped to provide ideal operating conditions.

NUPERCAINE

[1] Coller, F. A. and Ransom, H. K.: Carcinoma of the Rectum. Conclusions Based on 12 Years' Experience with Combined Abdominoperineal Resection. Surg., Gynec. & Obst., 78:304,1944.

* Trade Mark Reg. U.S. Pat. Off. Word "Nupercaine" identifies the product as alpha-butyloxy-cinchoninic acid—gamma-diethyl-ethylenediamide-hydrochloride.

★

CIBA PHARMACEUTICAL PRODUCTS, INC.
SUMMIT, NEW JERSEY
IN CANADA, CIBA COMPANY LIMITED, MONTREAL